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(71) Applicant:

Dr. Karl Thomae GmbH, 88400 Biberach, DE

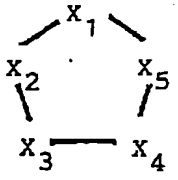
(72) Inventor:

Linz, Günter, Dipl.-Chem. Dr., 7951 Mittelbiberach, DE; Himmelsbach, Frank, Dipl.-Chem. Dr., 7951 Mittelbiberach, DE; Austel, Volkhard, Dipl.-Chem. Dr., 7950 Biberach, DE; Pieper, Helmut, Dipl.-Chem. Dr., 7950 Biberach, DE; Müller, Thomas, Dipl.-Chem. Dr., 7950 Biberach, DE; Weisenberger, Johannes, Dipl.-Chem. Dr., 7950 Biberach, DE; Guth, Brian, Dr., 7951 Warthausen, DE

(54) **5-Membered Heterocycles, Processes for Their Preparation, and Medicaments Containing These Compounds**

5-gliedrige Heterocyclen, Verfahren zu ihrer Herstellung und diese Verbindungen enthaltende Arzneimittel

(57) The invention relates to 5-membered heterocycles of the general formula



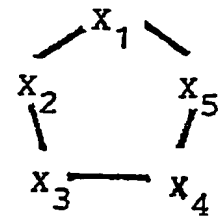
, (I)

in which
X_1 to X_5 are as defined in claim 1, the tautomers thereof, the stereoisomers thereof, including the mixtures and salts thereof, in particular the physiologically tolerable salts thereof, with inorganic or organic acids or bases, which have useful pharmacological properties, preferably aggregation-inhibiting effects, the medicaments containing the compounds, and processes for their preparation.

The following information has been taken from documents submitted by the applicant

Description

The invention relates to 5-membered heterocycles of the general formula



(I)

to tautomers thereof, to stereoisomers thereof, including mixtures and salts thereof, in particular physiologically tolerable salts thereof, with inorganic or organic acids or bases, which have useful pharmacological properties, inter alia, preferably aggregation-inhibiting effects, medicaments containing these compounds, and processes for their preparation.

In the above general formula I,

(i) with the proviso that the 5-membered heterocyclic ring is not a pyrrolidine, pyrroline, pyrrolinone, or pyrrolidinone ring and contains at least one carbon atom and

(ii) with the exception of the compounds of 3-(4-amidinophenyl)-1-[4-(2-amino-2-carboxyethyl)phenyl]-2H-pyrazol-5-one and 3-(4-amidinophenyl)-1-[4-(2-amino-2-methoxycarbonylethyl)phenyl]-2H-pyrazol-5-one,

one of the radicals X_1 to X_5 is a group of the formulas

A – B – C – N< ,
A – B – C – CH< or
A – B – C – C<, in which

A is a cycloalkyl group having 5 to 7 carbon atoms, which is optionally substituted by 1 to 4 alkyl groups or by a hydroxy, alkoxy, phenylalkoxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl, or phenylalkoxycarbonyl group, and in which an unsubstituted methylene group is replaced by the R_a-N< group, whereby

R_a is a hydrogen atom, an alkyl group, an alkoxycarbonyl group having a total of 2 to 6 carbon atoms, a phenylalkoxycarbonyl group, an alkenyloxycarbonyl group having a total 4 to 6 carbon atoms, a cycloalkoxycarbonyl group having a total 6 to 8 carbon atoms, or an R_1-CO-O-(R_2CH)-O-CO- group,

in which

R_1 is an alkyl group having 1 to 5 carbon atoms, a cycloalkyl group having 5 to 7 carbon atoms, a phenylalkyl group, an alkoxy group having 1 to 5 carbon atoms, a cycloalkoxy group having 5 to 7 carbon atoms, or a phenyl group, and

R_2 is a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, a cycloalkyl group having 5 to 7 carbon atoms, or a phenyl group,

and additionally in the 6- or 7-membered azacycloalkyl groups thus formed a >CH- unit in the 4-position can be replaced by a nitrogen atom or in the 5- to 7-membered azacycloalkyl groups thus formed, a $-CH_2-CH<$ unit by a $-CH=C<$ unit, and in the piperazinyl or homopiperazinyl rings thus formed, a methylene group, which is adjacent to the nitrogen atom in the 4-position, by a carbonyl group,

a pyridyl or quinuclidinyl group or also, if

D is an alkylene or alkenylene group, each having up to 8 carbon atoms, which is substituted by an $R_3R_4N-CO-NR_5-$ or $R_6-SO_2-NR_3-$ group, in which

R_3 to R_5, which may be identical or different, each is a hydrogen atom or an alkyl or phenylalkyl group, and

R_6 is an alkyl group having 1 to 5 carbon atoms or a phenylalkyl or phenyl group,

or E is straight-chain or branched alkylene or alkenylene group, each of which has up to 5 carbon atoms, which is substituted by a hydroxy, alkoxy, alkylsulfenyl, R_3R_4N-, R_3O-CO-, R_6CO-NR_3-, $R_6O-CO-NR_3-$, $R_6SO_2-NR_3-$, or R_3R_4 N-CO-NR_5- group, in which R_3 to R_6 are defined as mentioned above,

a phenyl group, which is substituted in the 4-position by an R_aNH-CH_2- or $R_aNH-C(=NH)-$ group, or a phenyl group, to which an n-alkylene bridge having 3 or 4 carbon atoms, which is substituted by an R_aNH group, is attached via two adjacent carbon atoms, whereby R_a is defined in each case as mentioned above,

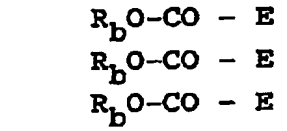
B is a bond, an alkyl group or an $-OCH_2-$, $-CH_2O-$, $-SCH_2-$, $-CH_2S-$, $-CONR_3-$, $-R_3NCO-$, $-CH_2NR_3-$, $-NR_3CH_2-$, $-SO_2NR_3-$, or $-NR_3SO_2-$ group, whereby R_3 is defined as mentioned above and an oxygen or nitrogen atom of the radical B is not bonded directly to a nitrogen atom of the radical A or the 5-membered heterocycle,

C is a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms or by alkyl, trifluoromethyl, hydroxy, alkoxy, alkylsulfenyl, alkylsulfinyl, or alkylsulfonyl groups, whereby the substituents may be identical or different,

a pyridinylene, pyrimidinylene, pyrazinylene, or pyridazinylene group, each of which can be substituted in the carbon skeleton by a chlorine atom or by an alkyl or alkoxy group,

a 1,4-cyclohexylene, 1,3-piperidinylene, 1,4-piperidinylene, or 1,4-piperazinylene group, or also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas



or

in which

D is a -CO-NR_3-, -NR_3-CO-, -SO_2-NR_3-, or -NR_3-SO_2-group, a straight-chain or branched alkylene or alkenylene group, which is optionally substituted by a hydroxy, alkoxy, alkylsulfenyl, R_3R_4N-, R_3O-CO-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or R_3R_4N-CO-NR_5- group, and in which in each case the alkylene moiety can contain 1 to 8 carbon atoms and the alkenylene moiety 2 to 8 carbon atoms, and R_3 to R_6 are defined as mentioned above,

a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms, or by alkyl, trifluoromethyl, hydroxy, alkoxy, alkylsulfenyl, alkylsulfinyl, or alkylsulfonyl groups,

a pyridinylene, pyrimidinylene, pyrazinylene, pyridazinylene, or triazenylene group, each of which can be substituted in the carbon skeleton by a chlorine atom or by an alkyl or alkoxy group, whereby additionally one or two -CH=N- groups each can be replaced by a -CO-NR_3- group, in which R_3 is defined as mentioned above, and then one of the nitrogen atoms can also be bonded to the radical E, instead of to the radical R_3, if E is not a bond and is not bonded via an oxygen or sulfur atom to the radical D, or to the atom, in the ring, of the respective radical X_1 to X_5,

a cycloalkylene group having 4 to 5 carbon atoms, which is optionally substituted by an alkyl, phenylalkyl, or phenyl group and in which a >CH- unit can be replaced by a nitrogen atom and additionally a methylene group, adjacent to the nitrogen atom, by a carbonyl group,

a cycloalkylene group having 6 or 7 carbon atoms, which is optionally substituted by an alkyl, phenylalkyl, or phenyl group and in which one or two >CH- units can each be replaced by a nitrogen atom, whereby additionally in each case one or two methylene groups, adjacent to a nitrogen atom, can be replaced by a carbonyl group, or

an alkylene group having 1 to 5 carbon atoms, which is linked via the radical W_1 to the atom, in the ring, of the respective radical X_1 to X_5 and in which W_1 is an NR_3 group, in which R_3 is defined as mentioned above, or an oxygen or sulfur atom, whereby an oxygen or sulfur atom of the radical W_1 may not be bonded directly to a nitrogen atom of the 5-membered heterocycle,

E is a bond,

a straight-chain or branched alkylene or alkenylene group, which is optionally substituted by a hydroxy, alkoxy, alkylsulfenyl, R_3R_4N-, R_3O-CO-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or

R_3R_4N-CO-NR_5- group and in which in each case the alkylene moiety can contain 1 to 5 carbon atoms and the alkenylene moiety 2 to 5 carbon atoms, and R_3 to R_6 are defined as mentioned above, or

an alkylene group, which is linked via the radical W_2 to the radical D and in which W_2 is an oxygen or sulfur atom, a sulfinyl, sulfonyl, -NR_3-, -(R_6CO)N-, -(R_6SO_2)N-, -$CONR_3$-, or -NR_3CO- group, in which R_3 and R_6 are defined as mentioned above, and whereby an oxygen or sulfur atom of the radical W_2 is not bonded directly to a nitrogen atom of the radical D, and

R_b is a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, or an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are defined as mentioned above,

a third of the radicals X_1 to X_5 is a sulfur atom,

HN<, R_6N<, R_7C< or $(R_7)_2$C< group

or a N atom, whereby R_6 is as defined at the outset and R_7 is a hydrogen atom, an alkyl, phenylalkyl, phenyl, alkoxy, R_3R_4N-, R_3O-CO-, or R_3R_4N-CO- group, whereby R_3 and R_4 are defined as mentioned above,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or an

R_7C< group,

in which R_7 is defined as mentioned above, or is also a carbonyl group, when it is not located between two nitrogen atoms,

a fifth of the radicals X_1 to X_5 is a nitrogen atom, an

R_7C< or $(R_7)_2$C<- group,

whereby R_7 is defined as mentioned above,

or also two adjacent radicals of the radicals X_1 to X_5 together are an o-phenylene group, whereby, if it was not specified otherwise,

the aforementioned alkyl, alkylene, or alkoxy moieties each can contain 1 to 3 carbon atoms.

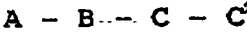
The aforementioned general formula I thus includes, for example, the appropriately substituted furan, tetrahydrofuran, 2,3-dihydrofuran, 2,5-dihydrofuran, thiophene, 2,3-dihydrothiophene, 2,5-dihydrothiophene, tetrahydrothiophene, 1,2-dithiolane, 1,3-dithiolane, pyrrole, indole, isoindole, 2,3-dihydroindole, 2,3-dihydroisoindole, 2-indolone, imidazole, 4,5-dihydroimidazole, tetrahydroimidazole, benzimidazoline, pyrazole, 2H-pyrazol-5-one, 4,5-dihydropyrazole, 1,5-dihydropyrazole, indazole, 2,3-dihydroindazole, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiazoline, thiazolidine, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, and tetrazole derivatives.

Preferred compounds of the above general formula I are those in which

one of the radicals X_1 to X_5 is a group of the formulas

A – B – C – N< ,

A – B – C – CH< or



in which

A is a cycloalkyl group having 5 to 7 carbon atoms, which is optionally substituted by 1 to 4 alkyl groups or by a hydroxyl, alkoxy, cyano, aminocarbonyl, carboxyl, or alkoxycarbonyl group, and in which an unsubstituted methylene group is replaced by the R_a-N< group, whereby

R_a is a hydrogen atom, an alkyl group, an alkoxycarbonyl group having a total of 2 to 6 carbon atoms, a phenylalkoxycarbonyl group, a cycloalkoxycarbonyl group having a total 6 to 8 carbon atoms, or an

R_1-CO-O-(R_2CH)-O-CO- group,

in which

R_1 is an alkyl group, a cycloalkyl group having 5 to 7 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a cycloalkoxy group having 5 to 7 carbon atoms, or a phenyl group, and

R_2 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms,

and additionally in the 6- or 7-membered azacycloalkyl groups thus formed, a >CH- unit in the 4-position can be replaced by a nitrogen atom or in the 5- to 7-membered azacycloalkyl groups thus formed, a -CH_2-CH< unit by a -CH=C< unit

a pyridyl or quinuclidinyl group or also, if

D is an alkylene group having 1 to 5 carbon atoms, which is substituted by an R_3R_4N-CO-NR_5- or R_6-SO_2-NR_3- group, in which

R_3 to R_5, which may be identical or different, each is a hydrogen atom or an alkyl or phenylalkyl group, and

R_6 is an alkyl group having 1 to 5 carbon atoms or a phenylalkyl or phenyl group,

or E is a straight-chain or branched alkylene group, each having 1 to 5 carbon atoms, which is substituted by an R_3R_4N-, R_6CO-NR_3-, R_6SO_2-NR_3-, R_3R_4N-CO-NR_5-, hydroxy, or alkoxy group, in which R_3 to R_6 are defined as mentioned above,

a phenyl group, which is substituted in the 4-position by an R_aNH-CH_2- or R_aNH-C(=NH)- group, or a phenyl group, to which an n-propylene or n-butylene bridge is attached via positions 3 and 4, whereby the n-propylene- and n-butylene bridge is substituted by an R_aNH- group and R_a in each case is defined as mentioned above,

B is a bond, a -CH_2-CH_2-, -OCH_2-, -CH_2O-, -$CONR_3$-, or -R_3NCO- group, whereby R_3 is defined as mentioned above and an oxygen or nitrogen atom of the radical B is not bonded directly to a nitrogen atom of the radical A or the 5-membered heterocycle,

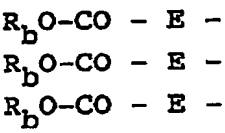
C is a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms or by alkyl, trifluoromethyl, hydroxy, or alkoxy groups, whereby the substituents may be identical or different,

a pyridinylene, pyrimidinylene, pyrazinylene, or pyridazinylene group, each of which can be substituted in the carbon skeleton by an alkyl or alkoxy group,

a 1,4-cyclohexylene, 1,4-piperidinylene, or 1,4-piperazinylene group, or

also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas



or

in which

D is a -CO-NR_3- or -NR_3-CO- group, a straight-chain or branched alkylene or alkenylene group which is optionally substituted by a hydroxy, alkoxy, R_3R_4N-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or R_3R_4N-CO-NR_5- group, and in which in each case the alkylene moiety can contain 1 to 5 carbon atoms and the alkenylene moiety 2 to 5 carbon atoms, and R_3 to R_6 are defined as mentioned above,

a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms or by alkyl, trifluoromethyl, hydroxy, or alkoxy groups,

a pyridinylene, pyrimidinylene, pyrazinylene, or pyridazinylene group, each of which can be substituted in the carbon skeleton by an alkyl or alkoxy group,

a cyclohexylene group, in which one or two >CH- units can each be replaced by a nitrogen atom, whereby additionally a methylene group, adjacent to a nitrogen atom, can be replaced by a carbonyl group, or

an alkylene group having 1 to 4 carbon atoms, which is linked via the radical W_1 to the atom, in the ring, of the respective radical X_1 to X_5 and in which W_1 is an NR_3- group, in which R_3 is defined as mentioned above, or an oxygen or sulfur atom, whereby an oxygen or sulfur atom of the radical W_1 may not be bonded directly to a nitrogen atom of the 5-membered heterocycle,

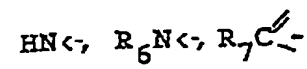
E is a bond,

a straight-chain or branched alkylene group having 1 to 5 carbon atoms, which is optionally substituted by a hydroxy, alkoxy, R_3R_4N-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or R_3R_4N-CO-NR_5- group, whereby R_3 to R_6 are defined as mentioned above, or

an alkylene group, which is linked via the radical W_2 to the radical D, and in which W_2 is an oxygen or sulfur atom, or an -NR_3-, -(R_6CO)N-, or -(R_6SO_2)N- group, in which R_3 and R_6 are defined as above, and whereby an oxygen or sulfur atom of the radical W_2 is not bonded directly to a nitrogen atom of the radical D, and

R_b is a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl group having 5 to 7 carbon atoms, or an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are defined as mentioned above,

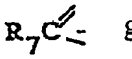
a third of the radicals X_1 to X_5 is an



or an $(R_7)_2C<$ group

or a N atom, whereby R_6 is as defined at the outset and R_7 is a hydrogen atom or an alkyl or phenyl group,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or a



group,

in which R_7 is defined as mentioned above,

a fifth of the radicals X_1 to X_5 is a nitrogen atom or an

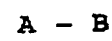
 or an $(R_7)_2C<$ group,

whereby R_7 is defined as mentioned above,

or also two adjacent radicals of the radicals X_1 to X_5 together are an o-phenylene group,

particularly those compounds, in which

one of the radicals X_1 to X_5 is a group of the formulas

 or

 , in which

A is a 1,3-pyrrolidinyl, 1,3-piperidyl, or 1,4-piperidyl group, optionally substituted in the carbon skeleton by 1 to 4 methyl groups or by a hydroxy, methoxy, cyano, or aminocarbonyl group, whereby the aforementioned azabicycles are substituted in the 1-position by the radical R_a and R_a is a hydrogen atom, a methyl group, an ethyl group, or an alkoxycarbonyl group having a total of 2 to 6 carbon atoms,

a 1,4-piperazinyl or 3,4-dehydro-1,4-piperidyl group, each of which is substituted in the 1-position by the radical R_a and R_a is defined as mentioned above,

a pyridyl or quinuclidinyl group or also, if

D is an ethylene group substituted by an R_6-SO_2-NR_3- group, in which

R_3 is a hydrogen atom, a methyl or ethyl group and

R_6 is an alkyl group having 1 to 5 carbon atoms or a phenyl group,

or E is an ethylene group, which is substituted by an amino, R_6CO-NR_3-, R_6SO_2-NR_3-, or hydroxy group, in which R_3 and R_6 are defined as mentioned above, and

R_4 and R_5, which may be identical or different, each is a hydrogen atom or a methyl or ethyl group,

a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group,

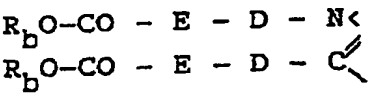
B is a bond, a -CH_2-CH_2-, -OCH_2-, -CH_2O-, -$CONR_3$-, or -R_3NCO- group, whereby R_3 is defined as mentioned above and an oxygen or nitrogen atom of the radical B is not bonded directly to a nitrogen atom of the radical A or the 5-membered heterocycle,

C is a phenylene group, which can be substituted by a chlorine atom or by a methyl group,

a pyridinylene, pyrimidinylene, or pyridazinylene group, or

also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas


or

, in which

D is a -CO-NR_3- or -NR_3-CO- group, whereby R_3 is defined as mentioned above, or a straight-chain or branched alkylene group having 1 to 5 carbon atoms,

a phenylene group, which may be substituted by a chlorine atom or a methyl group,

a 1,4-cyclohexylene group, or

an alkylene group having 1 to 4 carbon atoms, which is linked via an -NR_3- group, whereby R_3 is defined as mentioned above, to the atom, in the ring, of the respective radical X_1 to X_5,

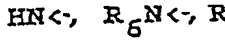
E is a bond,

an ethylene group optionally substituted by an R_6CO-NR_3- or R_6SO_2-NR_3- group, whereby R_3 and R_6 are defined as mentioned above, or

an -O-CH_2- or -NR_3-CH_2- group, whereby R_3 is defined as mentioned above, and

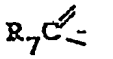
R_b is a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, or a cycloalkyl group having 5 or 6 carbon atoms,

a third of the radicals X_1 to X_5 is an


group

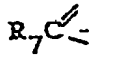
or a N atom, whereby R_6 is defined as mentioned above and R_7 is a hydrogen atom or a methyl or ethyl group,

a fourth of the radicals X_1 to $X_{[5]}$ is an oxygen, sulfur, or nitrogen atom, or an


group,

in which R_7 is defined as mentioned above,

a fifth of the radicals X_1 to X_5 is a nitrogen atom or an

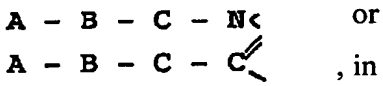

group,

whereby R_7 is defined as mentioned above,

or also two adjacent radicals of the radicals X_1 to X_5 together are an o-phenylene group,

tautomers thereof, stereoisomers thereof, including mixtures and salts thereof, in particular physiologically tolerable salts thereof, with inorganic or organic acids or bases.

Especially preferred compounds of the above general formula are, however, those compounds in which one of the radicals X_1 to X_5 is a group of the formulas


or

, in which

A is a 4-piperidyl group substituted in the 1-position by the radical R_a, whereby

R_a is a hydrogen atom or an alkoxycarbonyl group having a total of 2 to 6 carbon atoms,

or also, if

D is an ethylene group substituted by an R_6-SO_2-NR_3- group, in which

R_3 is a hydrogen atom and

R_6 is an alkyl group having 1 to 5 carbon atoms,

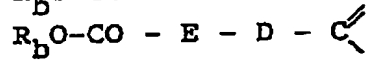
a phenyl group, which is substituted in the 4-position by an NH_2-C(=NH)- group,

B is a bond or a -CH_2-CH_2- or -CH_2O- group,

C is a phenylene group or also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas


or


, in which

D is a -CO-NH-group, an alkylene group having 1 to 5 carbon atoms, a phenylene group, or a 1,4-cyclohexylene group,

E is a bond or an ethylene group, and

R_b is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms,

a third of the radicals X_1 to X_5 is an

$R_6N<$- or  group

or a N atom, whereby R_6 is a phenyl group and R_7 a hydrogen atom or a methyl or ethyl group,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or a

 group,

in which R_7 is defined as mentioned above,

a fifth of the radicals X_1 to X_5 is a nitrogen atom,

tautomers thereof, stereoisomers thereof, including mixtures and salts thereof, in particular physiologically tolerable salts thereof, with inorganic or organic acids or bases:

The following are mentioned as particularly preferable compounds:

(i) 2-(*trans*-4-carboxycyclohexyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole,

(ii) 2-[*trans*-4-(methoxycarbonyl)cyclohexyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole,

(iii) 1-[6-(4-amidinophenyl)-3-pyridazinyl]-4-[2-(n-butanesulfonylamino)-2-carboxyethyl]imidazole, and

(iv) 1-[6-(4-amidinophenyl)-3-pyridazinyl]-4-[2-(n-butanesulfonylamino)-2-(methoxycarbonyl)ethyl]imidazole,

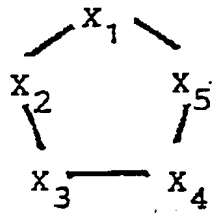
and the salts thereof.

According to the invention, the novel compounds are obtained, for example, by the following processes:

a) To prepare compounds of the general formula I, in which one of second of the radicals X_1 to X_5 is an

$R_bO-CO-E-D-C\overset{\diagup\!\!\diagup}{<}$ - or R_bO-CO-E-D-CH<- group:

Reaction of a compound of the general formula



(II)

in which

X_1 to X_5 are as defined at the outset with the proviso that a second of the radicals X_1 to X_5 is an

$HO-CO-C\overset{\diagup\!\!\diagup}{<}$ - or HO-CO-CH< group,

or the reactive derivatives thereof with a compound of the general formula

$R_bO - CO - E - HNR_3$ (III)

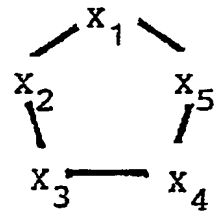
in which

R_3, R_b, and E are as defined at the outset.

The reaction is expediently carried out in a solvent or solvent mixture, such as methylene chloride, dimethylformamide, dimethyl sulfoxide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, or dioxane, optionally in the presence of a dehydrating agent, e.g., in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, 2-[(1H)-benzotriazolyl]-1,1,3,3-tetramethyluronium salts, N,N'-thionyldiimidazole, N,N'-carbonyldiimidazole, or

triphenylphosphine/carbon tetrachloride, optionally in the presence of dimethylaminopyridine or 1-hydroxybenzotriazole and/or a base such as triethylamine, N-ethyldiisopropylamine, or N-methylmorpholine, expediently at temperatures between –10 and 150 °C, preferably at temperatures between 0 and 50 °C.

b) To prepare compounds of the general formula I, in which R_a is a hydrogen atom: Removal of a protective group of a compound of the general formula



(IV)

in which

X_1 to X_5 are as defined at the outset with the proviso that R_a is an alkoxycarbonyl group having a total of 2 to 6 carbon atoms, a phenylalkoxycarbonyl group, an alkenyloxycarbonyl group having a total 4 to 6 carbon atoms, a cycloalkoxycarbonyl group having a total 6 to 8 carbon atoms, or a removable protective group for an imino group, such as the acetyl, trifluoroacetyl, benzoyl, benzyl, methoxybenzyl, or 2,4-dimethoxybenzyl group, by means of hydrolysis, hydrogenolysis, or thermolysis.

The hydrolysis is expediently carried out either in the presence of an acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, acetic acid/hydrochloric acid, trichloroacetic acid, or trifluoroacetic acid, or in the presence of a base, such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, in a suitable solvent, such as water, methanol, water/methanol, ethanol, water/ethanol, water/isopropanol, water/tetrahydrofuran, ether/dioxane or water/dioxane, at temperatures between –10 °C and 120 °C, e.g., at temperatures between room temperature and the boiling point of the reaction mixture.

In the acid hydrolysis, depending on the employed conditions, other hydrolytically cleavable groups as well, optionally present in a compound of the formula IV, such as alkoxycarbonyl or phenylalkoxycarbonyl groups can be cleaved simultaneously.

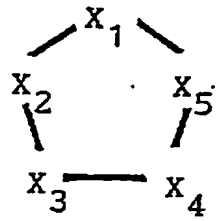
If, for example, R_a is the *tert*-butyloxycarbonyl group, the *tert*-butyl group can also be removed by treatment with an acid, such as trifluoroacetic acid, hydrochloric acid, formic acid, p-toluenesulfonic acid, sulfuric acid, phosphoric acid, or polyphosphoric acid, optionally in an inert solvent, such as methanol, methylene chloride, chloroform, benzene, toluene, tetrahydrofuran,

dioxane, ether/dioxane, or ether/dioxane/methanol, preferably at temperatures between –10 °C and 120 °C, e.g., at temperatures between 0 and 60 °C, or also thermally optionally in an inert solvent, such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran, or dioxane, and optionally in the presence of a catalytic amount of an acid, such as p-toluenesulfonic acid, sulfuric acid, phosphoric acid, or polyphosphoric acid, preferably at the boiling point of the employed solvent, e.g., at temperatures between 40 °C and 100 °C.

If, for example, R_a is the benzyloxycarbonyl group, the benzyl group can also be removed hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/carbon in a suitable solvent, such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane, or dimethylformamide, preferably at temperatures between 0 and 50 °C, e.g., at room temperature, and a hydrogen pressure of 1 to 10 bar. In the hydrogenolysis, other radicals, e.g., a nitro group, can be simultaneously reduced to an amino group or a benzyloxy group to a hydroxy group and a benzylamino group to an amino group. Additionally, present C=C double bonds can be simultaneously hydrogenated to single bonds.

c) To prepare compounds of the general formula I, in which R_b is a hydrogen atom:

Removal of a protective group of a compound of the general formula



(V)

in which

X_1 to X_5 are as defined at the outset with the proviso that R_b is an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, or a removable protective group for an carboxy group, such as the trimethylsilyl, methoxybenzyl, 2,4-dimethoxybenzyl, or tetrahydropyranyl group, by means of hydrolysis, hydrogenolysis, or thermolysis.

The hydrolysis is expediently carried out either in the presence of an acid, such as hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, acetic acid/hydrochloric acid, trichloroacetic acid, or trifluoroacetic acid, or in the presence of a base, such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, in a suitable solvent, such as water,

methanol, water/methanol, ethanol, water/ethanol, water/isopropanol, water/tetrahydrofuran, or water/dioxane, at temperatures between –10 °C and 120 °C, e.g., at temperatures between room temperature and the boiling point of the reaction mixture.

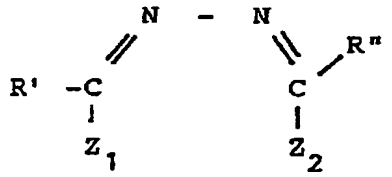
In the acid hydrolysis, depending on the employed conditions, other hydrolytically removable groups as well, optionally present in a compound of the formula V, such as the acetyl, trifluoroacetyl, benzoyl, *tert*-butyloxycarbonyl, or benzyloxycarbonyl group, can be removed simultaneously.

If, for example, R_b is the *tert*-butyl group, the *tert*-butyl group can also be removed by treatment with an acid, such as trifluoroacetic acid, hydrochloric acid, formic acid, p-toluenesulfonic acid, sulfuric acid, phosphoric acid, or polyphosphoric acid, optionally in an inert solvent, such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran, or dioxane, preferably at temperatures between –10 °C and 120 °C, e.g., at temperatures between 0 and 60 °C, or also thermally optionally in an inert solvent, such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran, or dioxane, and optionally in the presence of a catalytic amount of an acid, such as p-toluenesulfonic acid, sulfuric acid, phosphoric acid, or polyphosphoric acid, preferably at the boiling point of the employed solvent, e.g., at temperatures between 40 °C and 100 °C.

If, for example, R_b is the benzyl group, the benzyl group can also be removed hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/carbon in a suitable solvent, such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane, or dimethylformamide, preferably at temperatures between 0 and 50 °C, e.g., at room temperature and at a hydrogen pressure of 1 to 10 bar. In the hydrogenolysis, other radicals, e.g., a nitro group, can be simultaneously reduced to an amino group or a benzyloxy group to a hydroxy group and a benzylamino or benzyloxycarbonylamino group to an amino group. Additionally, the C=C double bond can be simultaneously hydrogenated to single bonds.

d) To prepare 1,3,4-oxadiazole, 1,2,4-triazole, and 1,3,4-thiadiazole derivatives of the general formula I:

Cyclization of a compound optionally formed in the reaction mixture of the general formula



(VI)

in which

Z_1 and Z_2, which may be identical or different, are halogen atoms, amino groups optionally substituted by R_6, hydroxy, alkoxy, mercapto, or alkylmercapto groups, one of the radicals R' or R" is an A-B-C- group and the other of the radicals R' or R" an R_bO-CO-E-D group, and, if necessary, subsequent alkylation.

The reaction is expediently carried out in a solvent, such as tetrahydrofuran, dioxane, 1,2-dichlorobenzene, or pyridine, at temperatures up to boiling point of the employed solvent, e.g., at temperatures between 20 and 180 °C.

If, in a compound of the general formula VI, Z_1 and Z_2 each are a hydroxy group, to prepare a 1,3,4-oxadiazole derivate the reaction is carried out preferably in the presence of a dehydrating agent such as thionyl chloride,

to prepare a 1,3,4-thiadiazole derivate, the reaction is carried out preferably in the presence of a sulfur-introducing reagent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, and

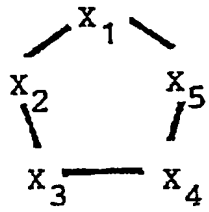
to prepare a 1,3,4-triazole derivate, the reaction is carried out preferably in the presence of a halogen-introducing agent such as phosphorus trichloride and in the presence of aniline.

To prepare the other 1,2,4-triazole derivatives, a compound of the general formula VI, in which one of the radicals Z_1 or Z_2 is a hydroxy group and the other of the radicals Z_1 or Z_2 an amino group, is cyclized and, if necessary, then alkylated.

The subsequent alkylation is expediently carried out in a solvent, such as methylene chloride, tetrahydrofuran, dioxane, dimethyl sulfoxide, or dimethylformamide, optionally in the presence of a base, such as sodium bicarbonate, potassium carbonate, or sodium hydroxide solution, or in the presence of a tertiary organic base such as N-ethyldiisopropylamine or N-methylmorpholine, which can function simultaneously as the solvent, at temperatures between –30 and 100 °C, but preferably at temperatures between –10 and 80 °C.

e) To prepare compounds of the general formula I, in which A is a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group:

Reaction of a compound, optionally formed in the reaction mixture, of the general formula



(VII)

in which

X_1 to X_5 are as defined at the outset with the proviso that A is a phenyl group, which is substituted in the 4-position by a Z_3-C(=NH)- group, whereby Z_3 is an alkoxy or aralkoxy group, such as the methoxy, ethoxy, n-propoxy, isopropanol, or benzyloxy group, or an alkylthio or aralkylthio group, such as the methylthio, ethylthio, n-propylthio, or benzylthio group, or an amino group, with an amine of the general formula

R_a'-NH_2 (VIII)

in which

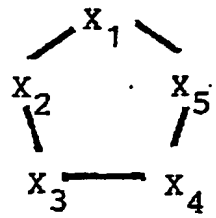
R_a' is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms.

The reaction is expediently carried out in a solvent, such as methanol, ethanol, n-propanol, water, methanol/water, tetrahydrofuran, or dioxane, at temperatures between 0 and 150 °C, preferably at temperatures between 20 and 120 °C, with an appropriate free amine or with an appropriate acid addition salt such as, for example, ammonium carbonate or ammonium acetate.

A compound of the general formula VII is obtained, for example, by reacting an appropriate nitrile with an appropriate alcohol, such as methanol, ethanol, n-propanol, isopropanol, or benzyl alcohol, in the presence of an acid such as hydrochloric acid or in the presence of an appropriate alcoholate such as sodium methylate or sodium ethylate, or by reacting an appropriate amide with a trialkyloxonium salt such as triethyloxonium tetrafluoroborate in a solvent, such as methylene chloride, tetrahydrofuran, or dioxane, at temperatures between – 10 and 50 °C, but preferably at temperatures between 0 and 20 °C, or an appropriate nitrile with hydrogen sulfide expediently in a solvent such as pyridine or dimethylformamide and in the presence of a base such as triethylamine and subsequent alkylation of the formed thioamide with an appropriate alkyl or aralkyl halide.

f) To prepare compounds of the general formula I, in which A is a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)-group:

Reaction of a compound of the general formula



(IX)

in which

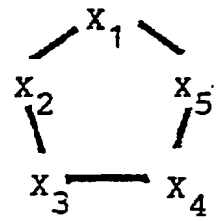
X_1 to X_5 are as defined at the outset with the proviso that A is a phenyl group, which is substituted in the 4-position by a cyano group, with hydroxylamine and subsequent reduction of the thus obtained amidoxime.

The reaction with hydroxylamine is expediently carried out in a solvent, such as methanol, ethanol, n-propanol, water, methanol/water, ethanol/water, tetrahydrofuran, or dioxane, optionally with addition of a base such as, e.g., sodium bicarbonate at temperatures between 0 and 100 °C, but preferably at temperatures between 20 and 80 °C either with free hydroxylamine or with an appropriate acid addition salt such as, for example, the hydrochloride.

The subsequent reduction is carried out preferably in a suitable solvent, such as methanol, methanol/ water, methanol-ammonia, methanol/water/ammonia, methanol/hydrochloric acid, ethanol, ether, tetrahydrofuran, dioxane, dimethylformamide, or glacial acetic acid, in the presence of catalytically excited hydrogen, e.g., of hydrogen in the presence of Raney nickel, platinum, or palladium/carbon, at temperatures between 0 and 100 °C, preferably at temperatures between 20 and 80 °C.

g) To prepare compounds of the general formula I, in which A is a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group:

Reaction of a compound of the general formula



(IX)

in which

X_1 to X_5 are as defined at the outset with the proviso that A is a phenyl group, which is substituted in the 4-position by a cyano group, with an appropriate alkylchloroaluminum amide.

The reaction is carried out preferably in a suitable solvent, for example, in benzene or toluene at temperatures between 0 and 100 °C, but preferably at a temperature between 20 and 80 °C and

the thus obtained aluminum complex is then hydrolytically broken down, preferably with the aid of a slurry of silica gel in chloroform (see R. S. Garigipati, Tetrahedron Letters 31, 1969 (1990)).

h) To prepare 1,3-thiazoles and imidazoles of the general formula I:

Reaction of a compound of the general formula

$R'\text{-}CO\text{-}CH_2\text{-}Z_4$ (X)

with a compound of the general formula

$R''\text{-}CU\text{-}NH_2$ (XI)

in which

one of the radicals R' or R" is an A-B-C group and

the other of the radicals R' or R" an $R_bO\text{-}CO\text{-}E\text{-}D$ group,

Z_4 is a nucleophilic leaving group, such as a chlorine, bromine, or iodine atom, and

U is a sulfur atom or an imino group.

The reaction is expediently carried out in a solvent such as methanol, ethanol or isopropanol, optionally in the presence of a base such as sodium bicarbonate at elevated temperatures, e.g., at the boiling point of the employed solvent.

i) To prepare compounds of the general formula I, in which R_a, with the exception of the hydrogen atom, is as defined at the outset and B is a $-CH_2O-$ group:

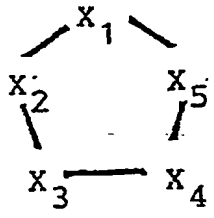
Reaction of a compound of the general formula

$A\text{-}CH_2\text{-}Z_5$ (XII)

in which

A is as defined at the outset with the proviso that R_a, with the exception of the hydrogen atom, is as defined at the outset, and

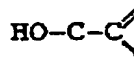
Z_5 is a nucleophilic leaving group such as a halogen atom or a sulfonyloxy group, e.g., a methanesulfonyloxy group, or a chlorine or bromine atom, with a compound of the general formula



(XIII)

in which

X_1 to X_5 are as defined at the outset with the proviso that a second of the radicals X_1 to X_5 is an

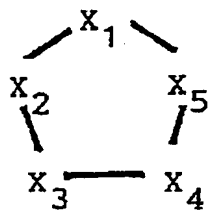
HO-C-CH< or  group,

whereby C is as defined at the outset, or with the alkali or alkaline earth metal salts thereof, such as the lithium, sodium, potassium, cesium, magnesium, or calcium salts.

The reaction is expediently carried out in a solvent, such as tetrahydrofuran, acetone, dioxane, dimethyl sulfoxide, sulfolane, dimethylformamide, or dimethylacetamide, in the presence of an inorganic base, such as potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, sodium hydroxide, or potassium *tert*-butylate, or in the presence of tertiary organic bases such as N-ethyl-diisopropylamine, which can optionally also function as the solvent, and optionally in the presence of a phase transfer catalyst such as polyethylene glycol 750 monomethyl ether on polystyrene or hexadecyltrimethylammonium chloride at temperatures between 0 and 180 °C, but preferably at temperatures between 10 and 160 °C.

j) To prepare compounds of the general formula I, in which one of the radicals X_1 to X_5 is an A-B-C-N< or R_bO-CO-E-D-N< group:

Alkylation of a compound of the general formula



(XIV)

in which

X_1 to X_5 are as defined at the outset with the proviso that one of the radicals X_1 to X_5 is an imino group, with a compound of the general formula

$W\text{-}Z_6$ (XV)

in which

W is an A-B-C or R_bO-CO-E-D group, whereby A to D are defined as mentioned at the outset, and

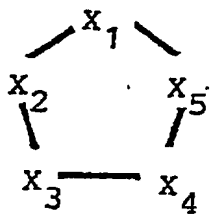
Z_6 is a nucleophilic leaving group such as a halogen atom or a sulfonyloxy group, e.g., a methanesulfonyloxy group, or a chlorine or bromine atom.

The alkylation is expediently carried out in a solvent or solvent mixture, such as methylene chloride, dimethylformamide, dimethyl sulfoxide, benzene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, or dioxane, in the presence of an acid-binding agent, e.g., an alcoholate such as potassium *tert*-butylate, an alkali hydroxide such as sodium or potassium hydroxide, an

alkali carbonate such as potassium carbonate, an alkali amide such as sodium amide, or an alkali hydride, expediently at temperatures between –0 and 150 °C, preferably at temperatures between 0 and 50 °C.

k) To prepare compounds of the general formula I, in which R_b is an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are defined as mentioned above, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety:

Esterification of a compound of the general formula



(XVI)

in which

X_1 to X_5 are as defined at the outset with the proviso that R_b is a hydrogen atom, with a compound of the general formula

Z_7-R_b' (XVII)

in which

R_b' is an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are as defined at the outset, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, and

Z_7 a hydroxy group or a nucleophilic leaving group such as a halogen atom or a sulfonyloxy group, e.g., a chlorine, bromine, or iodine atom, a methanesulfonyloxy or p-toluenesulfonyloxy group.

The esterification is expediently carried out in a suitable solvent, e.g., in an appropriate alcohol, such as methanol, ethanol, or isopropanol, methylene chloride, tetrahydrofuran, dioxane, pyridine, toluene, or dimethyl sulfoxide, in the presence of an acid-activating and/or dehydrating agent, such as hydrogen chloride, conc. sulfuric acid, thionyl chloride, ethyl chloroformate, carbonyldiimidazole, or N,N'-dicyclohexylcarbodiimide, or the isourea esters thereof, optionally in the presence of a reaction accelerator, such as copper chloride, by transesterification, e.g., with

an appropriate dicarbonate, or by reaction with an appropriate halide, preferably in the presence of a base such as potassium carbonate and optionally in the presence of a reaction accelerator such as potassium iodide at temperatures between 0 and 100 °C, but preferably at temperatures between 20 °C and the boiling point of the solvent concerned.

If Z_7 is a nucleophilic leaving group, the reaction is preferably carried out with an alkali salt of a compound of the general formula XVI.

In the reactions described above, reactive groups, which may be present, such as hydroxy, carboxy, amino, alkylamino, or imino groups, are protected during the reaction by customary protective groups, which are removed again after the reaction.

For example, a suitable protective radical for a hydroxy group is the trimethylsilyl, acetyl, benzoyl, *tert*-butyl, trityl, benzyl, or tetrahydropyranyl group,
a suitable protective radical for a carboxyl group is the trimethylsilyl, methyl, ethyl, *tert*-butyl, benzyl, or tetrahydropyranyl group, and
a suitable protective radical for an amino, alkylamino, or imino group is the acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl, or 2,4-dimethoxybenzyl group, and for the amino group, additionally the phthalyl group.

An employed protective radical is optionally removed subsequently, for example, hydrolytically in an aqueous solvent, e.g., in water, isopropanol/water, tetrahydrofuran/water, or dioxane/water, in the presence of an acid, such as trifluoroacetic acid, hydrochloric acid, or sulfuric acid, or in the presence of an alkali metal base, such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, or by means of ether cleavage, e.g., in the presence of iodotrimethylsilane, at temperatures between 0 and 100 °C, preferably at temperatures between 10 and 50 °C.

However, a benzyl, methoxybenzyl, or benzyloxycarbonyl radical is removed, for example, hydrogenolytically, e.g., with hydrogen in the presence of a catalyst such as palladium/carbon in a solvent, such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone, or glacial acetic acid, if appropriate, with addition of an acid such as hydrochloric acid, at temperatures between 0 and 50 °C, but preferably at room temperature and at a hydrogen pressure of 1 to 7 bar, but preferably of 3 to 5 bar.

The removal of a methoxybenzyl group can also occur in the presence of an oxidizing agent such as cerium(IV) ammonium nitrate in a solvent, such as methylene chloride, acetonitrile, or acetonitrile/water, at temperatures between 0 and 50 °C, but preferably at room temperature.

However, the removal of a 2,4-dimethoxybenzyl radical is preferably carried out in trifluoroacetic acid in the presence of anisole.

A *tert*-butyl or *tert*-butyloxycarbonyl radical is preferably removed by treatment with an acid such as trifluoroacetic acid or hydrochloric acid, if appropriate, using a solvent such as methylene chloride, dioxane, or ether.

A phthalyl radical is preferably removed in the presence of hydrazine or a primary amine, such as methylamine, ethylamine, or n-butylamine, in a solvent, such as methanol, ethanol, isopropanol, toluene/water, or dioxane, at temperatures between 20 and 50 °C.

An allyloxycarbonyl radical is removed by treatment with a catalytic amount of tetrakis(triphenylphosphine)palladium(O), preferably in a solvent such as tetrahydrofuran and preferably in the presence of an excess of a base such as morpholine or 1,3-dimedone at temperatures between 0 and 100 °C, preferably at room temperature and under inert gas, or by treatment with a catalytic amount of tris(triphenylphosphine)rhodium(I) chloride in a solvent such as aqueous ethanol and, if appropriate, in the presence of a base such as 1,4-diazabicyclo[2.2.2]octane at temperatures between 20 and 70 °C.

Furthermore, the obtained compounds of the general formula I, as has already been mentioned at the outset, can be separated into their enantiomers and/or diastereomers. Thus, for example, *cis/trans* mixtures can be separated into their *cis* and *trans* isomers and chiral compounds into their enantiomers.

Thus, for example, the obtained *cis/trans* mixtures can be separated by chromatography into their *cis* and *trans* isomers, the obtained compounds of the general formula I, which occur as racemates, can be separated by methods known per se (see Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of the general formula I having at least 2 stereogenic centers can be separated on the basis of their physicochemical differences by methods known *per se*, e.g. by chromatography and/or fractional crystallization, into their diastereomers which, if they are obtained in racemic form, can then be separated as mentioned above into the enantiomers.

Separation of the enantiomers is preferably carried out by column separation on chiral phases or by recrystallization from an optically active solvent or by reaction with an optically active

substance, forming salts or derivatives such as, e.g., esters or amides with the racemic compound, in particular acids and their activated derivatives or alcohols, and separation of the diastereomeric salt mixture or derivative obtained in this way, e.g., on the basis of differing solubilities, whereby the free antipodes can be liberated from the pure diastereomeric salts or derivatives by the action of suitable agents. Particularly customary, optically active acids are, e.g., the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulfonic acid, glutamic acid, aspartic acid, or quinic acid. A suitable optically active alcohol is, for example, (+)- or (–)-menthol and a suitable optically active acyl radical in amides is, for example, (+)- or (–)-menthyloxycarbonyl.

In addition, the obtained compounds of the formula I can be converted into their salts, in particular, for pharmaceutical administration, into their physiologically tolerable salts with inorganic or organic acids. Suitable acids for this purpose are, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

Additionally, the novel compounds of the formula I thus obtained, if these contain a carboxyl group, can, if desired, then be converted into their addition salts with inorganic or organic bases, in particular, for pharmaceutical administration, into their physiologically tolerable salts. Suitable bases in this context are, for example, sodium hydroxide, potassium hydroxide, ammonia, cyclohexylamine, ethanolamine, diethanolamine, and triethanolamine.

The compounds used as starting substances are known from the literature in some cases or are obtained by processes known from the literature (see Examples I to XV).

As already mentioned at the outset, the novel 5-membered heterocycles of the general formula I and their salts, in particular, their physiologically tolerable salts, with inorganic or organic acids or bases have useful pharmacological properties, in addition to an anti-inflammatory and anti-osteoclastic effect, but in particular antithrombotic, antiaggregatory, and antitumor or antimetastatic effects. In this context, the compounds of the general formula I, in which R_a is one of the aforementioned oxycarbonyl radicals and/or R_b one of the aforementioned ester radicals, are prodrugs.

For example, the compounds of the general formula I were investigated for their biological effects as follows:

1. Competitive Binding of ^{3}H-BIBU 52/Test Substance to Human Platelets

A suspension of human platelets in plasma is incubated with ^{3}H-BIBU 52 [= (3S,5S)-5-[(4'-amidino-4-biphenyl)oxymethyl]-3-[(carboxy)methyl]-2-pyrrolidinone[3-^{3}H-4-biphenylyl]], which replaces the ligand known from the literature ^{125}I-fibrinogen, (see German Patent Application P 42 14 245.8 by the same applicant of 4/30/1992, internal reference: Case 5/1093-FL) and various concentrations of the substance to be tested. The free and bound ligand is separated by centrifugation and quantitatively determined by scintillation counting. From the measurements, the inhibition of ^{3}BIBU 52 binding by the test substance is determined.

For this purpose, donor blood is taken from an anticubital vein and anticoagulated with trisodium citrate (final concentration 13 mM). The blood is centrifuged at 170g for 10 minutes and the supernatant platelet-rich plasma (PRP) is removed. The remaining blood is intensely centrifuged off once more to obtain plasma. The PRP is diluted 1:10 with autologous plasma. 750 µL is incubated with 50 µL of physiological saline solution, 100 µL of test substance solution, 50 µL of ^{14}C-sucrose (3700 Bq), and 50 µL of ^{3}H-BIBU 52 (final concentration: 5 nM) at room temperature for 20 minutes. To measure the nonspecific binding, instead of the test substance, 5 µL of BIBU 52 (final concentration: 30 µM) is used. The samples are centrifuged for 20 seconds at 10,000g and the supernatant is removed. 100 µL of this is measured to determine the free ligand. The pellet is dissolved in 500 µL of 0.2N NaOH; 450 µL is combined with 2 mL of scintillator and 25 µL of 5N HCl and measured. The residual plasma still remaining in the pellet is determined from the ^{14}C content, and the bound ligand from the ^{3}H measurement. After removal of the nonspecific binding, the pellet activity is plotted against the test substance concentration and the concentration determined for a 50% inhibition of binding.

2. Antithrombotic effect

Methodology

Platelet aggregation is measured by the method of Born and Cross (J. Physiol. 170, 397 (1964)) in platelet-rich plasma of healthy subjects. To inhibit clotting, the blood is treated with sodium citrate, 3.14% in 1:10 volume ratio.

Collagen-induced aggregation

The course of the decrease in the optical density of the platelet suspension is measured and recorded photometrically after addition of the aggregation-inducing substance. The aggregation

rate is deduced from the angle of inclination of the density curve. The point on the curve at which the greatest light transmission exists is used to calculate the optical density.

The collagen concentration is selected to be as low as possible, but in such a way that a reaction curve with an irreversible course results. Commercially available collagen from Hormonchemie, Munich, is used. Before the addition of collagen, the plasma is incubated in each case for 10 minutes with the substance at 37 °C.

The EC_{50}, describing the concentration at which there is a 50% inhibition in the optical density, is determined from the concentration/effect curves.

The following table contains the results found:

Substance (Example No.)	Competitive Binding of ^{3}H-BIBU 52/ Test Substance to Human Platelets IC_{50} [nM]	Inhibition of Platelet Aggregation EC_{50} [nM]
2	24000.0	3000
2(3)	550.0	380
3	400.0	880
3(1)	6800.0	4400
3(3)	1.6	40
5	510.0	320
5(3)	11.0	100

The compounds of the invention are well tolerated, because, for example, no animals died during the intravenous administration of 30 mg/kg of the compounds of Examples 5 and 5(3) to 3 mice in each case.

Based on their inhibitor effect on cell-cell or cell-matrix interactions, the novel carboxylic acid derivatives of the general formula I and their physiologically tolerable addition salts are suitable for the control or prevention of illnesses in which relatively small or relatively large cell aggregates occur or cell-matrix interactions play a part, e.g., in the control or prevention of venous and arterial thromboses, cerebrovascular disorders, pulmonary embolisms, myocardial infarction, arteriosclerosis, osteoporosis, and metastasis of tumors, and the treatment of genetic or acquired disorders of the interaction of cells with each other or with solid structures. Furthermore, these compounds are suitable for concomitant therapy in thrombolysis with fibrinolytics or vascular interventions such as transluminal angioplasty or in the therapy of states of shock, psoriasis, diabetes, and inflammations.

For the control or prevention of the aforementioned illnesses, the i.v. or p.o. dose is between 0.1 μg and 30 mg/kg of body weight, preferably 1 μg to 15 mg/kg of body weight, with up to 4

doses per day. For this purpose, the compounds of the formula I, prepared as taught by the invention, can be incorporated, if appropriate in combination with other active substances such as thromboxane receptor antagonists and thromboxane synthesis inhibitors or combinations thereof, serotonin antagonists, α-receptor antagonists, alkyl nitrates such as glyceryl trinitrate, phosphodiesterase inhibitors, prostacyclin and its analogues, fibrinolytics such as tPA, prourokinase, urokinase, or streptokinase, or anticoagulants such as heparin, dermatan sulfate, activated protein C, vitamin K antagonists, hirudine, inhibitors of thrombin or other activated clotting factors, together with one or more inert customary vehicles and/or diluents, e.g., with corn starch, lactose, cane sugar, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose, or fat-containing substances such as solid fat or suitable mixtures thereof, in customary galenical preparations such as tablets, coated tablets, capsules, powders, suspensions, solutions, sprays, or suppositories.

The following examples are intended to illustrate the invention in greater detail:

Example 1

4-(4-Piperidyl)benzoic acid hydrochloride

157.4 g of oxalyl chloride is added dropwise to a solution of 63.0 g of 1-acetyl-4-phenylpiperidine in 1000 mL of methylene chloride with good stirring at –10 to –20 °C. Next, 46.7 g of aluminum chloride is added. The mixture is stirred for 1 hour at –10 °C and another 82.7 g of aluminum chloride is added. After another 2 hours, the cooling bath is removed and the mixture is stirred for 24 hours at room temperature. The reaction solution is stirred carefully into ca. 4 L of ice water and the aqueous phase is extracted twice with methylene chloride. The combined organic phases are washed with water, dried over sodium sulfate, and the solvent is removed under reduced pressure. The remaining residue is dissolved with vigorous stirring in 2.5 L of 2N sodium hydroxide solution. Ice is added to the dark aqueous solution and the solution is acidified with conc. hydrochloric acid. The precipitate is filtered with suction, washed with water, and heated to reflux in 2 L of 6N hydrochloric acid for 5 hours. The solvent is removed under reduced pressure. The remaining solid is triturated with a small amount of water and filtered with suction.

Yield: 40.5 g (54% of theoretical yield),

Melting point: >300 °C

R_f value: 0.07 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Example II

4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]benzoic acid

47.5 g of 4-(4-piperidyl)benzoic acid hydrochloride is added carefully to 16.4 g of sodium hydroxide in 300 mL of water. The suspension is diluted with 500 mL of dioxane and 250 mL of water. Next, 54.6 g of dicarboxylic acid di-*tert*-butyl ester is added batchwise. The mixture is stirred for 16 hours at room temperature. The precipitate is filtered with suction and the filtrate is partially concentrated by evaporation under reduced pressure. The precipitate and the remaining aqueous filtrate are isolated and diluted with 1 L of water. The aqueous phase adjusted to pH 2 with saturated potassium hydrogen sulfate solution and extracted twice with ethyl acetate. The combined acetate phases are washed with saturated sodium chloride solution and dried over sodium sulfate, and the solvent is removed under reduced pressure. The crystalline crude product is triturated with a small amount of ethyl acetate, filtered with suction, and dried.

Yield: 54.0 g (90% of theoretical yield),

Melting point: 172-174 °C

R_f value: 0.73 (silica gel; ethyl acetate/cyclohexane = 4:1)

Example III

4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]benzoic acid hydrazide

9.6 g of 1-hydroxy-(1H)-benzotriazole and 17.4 g of N,N'-dicyclohexylcarbodiimide are added to a solution of 21.3 g of 4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl]benzoic acid in 150 mL of dimethylformamide at –10 °C. The mixture is stirred for 15 minutes at –10 °C, the cooling bath is removed, and the temperature is allowed to come to room temperature. This reaction solution is then added dropwise to a solution, cooled to –10 °C, of 50 mL of 80% hydrazine hydrate in 150 mL of dimethylformamide. The mixture is stirred for 16 hours at room temperature and the precipitate is filtered with suction. The filtrate is concentrated under reduced pressure. Water is added to the residue and the aqueous phase is extracted three times with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is evaporated under reduced pressure. The remaining solid is chromatographed with ethyl acetate/cyclohexane (4:1) over silica gel. 18.5 g of a crystalline solid is obtained, which is triturated with ethyl acetate and then filtered with suction.

Yield: 12.7 g (57% of theoretical yield),

Melting point: 151-154 °C

R_f value: 0.26 (silica gel; ethyl acetate/cyclohexane = 4:1)

Example IV

N-(4-(1-(*tert*-Butyloxycarbonyl)-4-piperidyl)benzoyl]-N'-[(methoxycarbonyl)carbonyl]hydrazine

A solution of 1.3 g of oxalic acid monomethyl ester chloride in 10 mL of anhydrous tetrahydrofuran is added dropwise to a solution of 3.2 g of 4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl]benzoic acid hydrazide and 1.7 g of ethyldiisopropylamine in 50 mL of anhydrous tetrahydrofuran with cooling in the ice bath. The mixture is stirred for 16 hours at room temperature, the precipitate is filtered with suction, and the filtrate is concentrated under reduced pressure. The residue is dissolved in ethyl acetate and washed once with 0.5N hydrochloric acid. The organic phase is dried and the solvent evaporated under reduced pressure. The crude product is chromatographed with ethyl acetate/cyclohexane (4:1) over silica gel.

Yield: 3.5 g (86% of theoretical yield),

Melting point: 105-108 °C

R_f value: 0.27 (silica gel; ethyl acetate/cyclohexane = 4:1)

The following compounds are obtained analogously:

(1) N-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]benzoyl]-N'-[[4-(methoxycarbonyl)-butyl]carbonyl]hydrazine

Adipic acid monomethyl ester chloride is used.

Melting point: 150-153 °C

R_f value: 0.26 (silica gel; ethyl acetate/cyclohexane = 4:1)

(2) N-[4-[4-(*tert*-Butyloxycarbonyl)-4-piperidyl]benzoyl]-N'-[[*cis*-4-(methoxycarbonyl)-cyclohexyl]carbonyl]hydrazine

cis-4-(Methoxycarbonyl)cyclohexane carboxylic acid chloride is used.

R_f value: 0.20 (silica gel; methylene chloride/methanol = 20:1)

(3) N-[4-[4-(*tert*-butyloxycarbonyl)-4-piperidyl]benzoyl]-N'-[[*trans*-4-(methoxycarbonyl)cyclohexyl]carbonyl]hydrazine.

A *cis/trans* mixture of 4-(methoxycarbonyl)cyclohexane carboxylic acid chloride is used.

The *trans* product precipitates from the organic phase.

Melting point: 198-201 °C

R_f value: 0.20 (silica gel; methylene chloride/methanol = 20:1)

Example V

2-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]phenyl]-5-methoxycarbonyl-1,3,4-thiadiazole

A solution of 3.32 g of N-[4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl]benzoyl]-N-[(methoxycarbonyl)carbonyl]hydrazine and 3.64 g of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in 60 mL of tetrahydrofuran is heated for 30 minutes to reflux. The solvent is removed under reduced pressure and the residue is chromatographed with ethyl acetate/cyclohexane (2:1) over silica gel.

Yield: 2.75 g (83% of theoretical yield),

Melting point: 143-146 °C

R_f value: 0.59 (silica gel; ethyl acetate/cyclohexane = 1:1)

Example VI

2-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]phenyl]-5-carboxy-1,3,4-thiadiazole

A solution of 2.7 g of 2-[4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl]phenyl]-5-methoxycarbonyl-1,3,4-thiadiazole and 1.1 g of lithium hydroxide hydrate in 50 mL of

tetrahydrofuran and 40 mL of water is stirred for 30 minutes at room temperature. The reaction solution is neutralized with 1N hydrochloric acid (pH 6.3).

The solvent is evaporated under reduced pressure and the residue is triturated with a small amount of water and filtered with suction.

Yield: 2.25 g (87% of theoretical yield),

R_f value: 0.42 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Example VII

4-[2-Amino-2-(methoxycarbonyl)ethyl)-1-(6-(4-cyanophenyl)-3-pyridazinyl]imidazole dihydrochloride

A solution of 9.6 g of N-*α*-*tert*-butyloxycarbonyl-L-histidine methyl ester in 100 mL of dry dimethylformamide is added dropwise to a suspension of 1.55 g of a 55% dispersion of sodium hydride in mineral oil in 50 mL of anhydrous dimethylformamide under a nitrogen atmosphere at 0 °C. The mixture is stirred for 30 minutes at 0 °C and then a solution of 7.6 g of 3-chloro-6-(4-cyanophenyl)pyridazine in 400 mL of dry dimethylformamide is added dropwise. The mixture is stirred for 2 hours at 0 °C and for 16 hours at room temperature. The reaction solution is poured onto an ice/sodium chloride solution and the aqueous phase is extracted three times with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is evaporated under reduced pressure. The residue is chromatographed with methylene chloride/methanol (20:1) over silica gel. After the solvent is removed, the thus obtained crude product (11.0 g) is dissolved in 500 mL of dioxane. 150 mL of ether saturated with hydrogen chloride is added and the precipitated precipitate is filtered with suction. The solid is dissolved in a mixture of 750 mL of dioxane, 750 mL of methanol, and 250 mL of ether saturated with hydrogen chloride and stirred for 16 hours at room temperature. Next, the precipitate is filtered with suction and washed with dioxane (yield of 4.4 g). Another 4.7 g of product is obtained by concentration of the mother liquor to ca. 100 mL and filtering of the precipitate with suction.

Total yield: 9.1 g (61% of theoretical yield),

Melting point: Sintering starting at 220 °C

R_f value: 0.43 (silica gel; methylene chloride/methanol/conc. ammonia = 9:1:0.1)

Example VIII

4-[2-(n-Butanesulfonylamino)-2-(methoxycarbonyl)ethyl]-1-[6-(4-cyanophenyl)-3-pyridazinyl]imidazole

A solution of 2.0 g of n-butanesulfonyl chloride in 20 mL of dimethylformamide is added dropwise to a solution of 4.2 g of 4-[2-amino-2-(methoxycarbonyl)ethyl]-1-[6-(4-cyanophenyl)-3-pyridazinyl]imidazole dihydrochloride and 4.5 g of ethyldiisopropylamine in 150 mL of methylene chloride at 0 °C. The mixture is stirred for 2 days at room temperature and the precipitate is then filtered with suction. The filtrate is washed twice with water. The organic phase is dried over sodium sulfate and the solvent is evaporated under reduced pressure. The residue is triturated with a small amount of methanol and filtered with suction.

Yield: 0.85 g (18% of theoretical yield),

R_f value: 0.49 (silica gel; methylene chloride/methanol/conc. ammonia = 9:1:0.1)

Example IX

1-(*tert*-Butyloxycarbonyl)-4-(2-cyanoethyl)piperidine

A suspension of 4.61 g of 1-(*tert*-butyloxycarbonyl)-4-[2-(methanesulfonyl)ethyl]piperidine, 10.5 g of potassium cyanide, and a spatula tip full of sodium iodide in 10 mL of anhydrous dimethylformamide is stirred for 16 hours at room temperature. After addition of a few milliliters of dimethylformamide, the mixture is heated for 7 hours to 70 °C. Ice water and 3 mL of 2N sodium hydroxide solution are added to the cooled suspension, and the aqueous phase is extracted repeatedly with *tert*-butyl methyl ether. The combined organic phases are washed with ice water and saturated sodium chloride solution and dried over sodium sulfate. The solvent is evaporated under reduced pressure.

Yield: 3.1 g (86% of the theoretical yield), yellowish oil

R_f value: 0.63 (silica gel; cyclohexane/glacial ethyl acetate = 1:1)

Example X

1-(*tert*-Butyloxycarbonyl)-4-[2-(aminothiocarbonyl)ethyl]piperidine

Hydrogen sulfide is passed through a solution of 3.0 g of 1-(*tert*-butyloxycarbonyl)-4-(2-cyanoethyl)piperidine in 15 mL of pyridine and 1.15 mL of triethylamine at a temperature of –5 to 0 °C for several minutes. The reaction solution is stirred for 16 hours at 0 °C and for another 24 hours at room temperature. Next, nitrogen is passed through the reaction solution for 3 hours. The solution is poured into 150 mL of an ice/water mixture and the aqueous phase is extracted twice with *tert*-butyl methyl ether. The combined organic extracts are washed successively twice with water, once with 2N citric acid solution, once with water, and once with saturated sodium chloride solution. The organic phase is dried and the solvent evaporated under reduced pressure.

A yellow oil is obtained, which is mixed with a small amount of cyclohexane. After addition of petroleum ether, the mixture is cooled in the ice/water bath and the precipitated colorless crystallizate is filtered with suction.

Yield: 550 g (16% of theoretical yield),

Melting point: 148-154 °C,

R_f value: 0.28 (silica gel; cyclohexane/glacial ethyl acetate = 1:1)

The following compounds are obtained analogous to Example X:

(1) 4-(Benzyloxy)benzoic acid thioamide

The reaction solution is poured into water and the precipitate is filtered with suction. The solid is dissolved in ethyl acetate and the solution is dried over sodium sulfate. After concentration of the solution under reduced pressure, the product precipitates.

Melting point: 172-174 °C

R_f value: 0.57 (silica gel; methylene chloride/ethyl acetate = 9:1)

Example XI

3-[4-(2-Chloroacetyl)phenyl]propionic acid ethyl ester

A solution of 23.7 g of chloroacetyl chloride is added dropwise to 56.0 g of aluminum trichloride in 150 mL of dichlorethane at 0 °C. Next, 35.6 g of ethyl 3-phenylpropionate is added dropwise, the temperature being kept between –5 and 5 °C. The mixture is stirred for 3 hours at room temperature. The reaction suspension is poured into a mixture of ice and 30 mL of concentrated hydrochloric acid, the phases are separated, and the aqueous phase is extracted twice with chloroform. The combined organic phases are washed with water and dried over magnesium sulfate. The solvent is evaporated under reduced pressure, mixed with petroleum ether, and filtered with suction.

Yield: 44.2 g (87% of the theoretical yield),

R_f value: 0.73 (silica gel; cyclohexane/glacial ethyl acetate = 1:1)

Example XII

2-[4-(Benzyloxy)phenyl]-4-[2-(methoxycarbonyl)ethyl]-1,3-thiazole

A solution of 14.0 g of 4-(benzyloxy)benzoic acid thioamide and 12.0 g of 4-bromo-3-oxobutane carboxylic acid methyl ester in 1000 mL of methanol is heated for 24 hours to reflux. The solvent is evaporated under reduced pressure and the residue is distributed between

methylene chloride and dilute sodium carbonate solution. The organic phase is shaken out once with dilute sodium carbonate solution and once with water and dried over sodium sulfate, and the solvent is evaporated under reduced pressure. The residue is recrystallized from methanol.

Yield: 15.0 g (74% of theoretical yield),

Melting point: 80 °C

R_f value: 0.25 (silica gel; methylene chloride/ethyl acetate = 19:1)

Example XIII

4-(2-Carboxyethyl)-2-(4-hydroxyphenyl)-1,3-thiazole

A solution of 8.0 g of 2-[4-(benzyloxy)phenyl]-4-[2-(methoxycarbonyl)ethyl]-1,3-thiazole in 200 mL of glacial acetic acid and 40 mL of methanol, saturated with hydrogen chloride, is hydrogenated in the presence of 4.0 g of 10% palladium on carbon for 1.5 hours at room temperature and at a hydrogen pressure of 5 bar. The catalyst is filtered off and the filtrate is concentrated by evaporation under reduced pressure. The residue is heated to boiling with ethyl acetate and cooled, and the precipitate filtered with suction.

Yield: 5.4 g (96% of theoretical yield),

Melting point: 224-226 °C

R_f value: 0.53 (silica gel; toluene/dioxane/ethanol/glacial acetic acid = 9:1:1:0.6)

Example XIV

2-(4-Hydroxyphenyl)-4-[2-(methoxycarbonyl) ethyl]-1,3-thiazole

A solution of 5.0 g of 4-(2-(carboxyethyl)-2-(4-hydroxyphenyl)-1,3-thiazole in 100 mL methanol and 10 mL of methanol saturated with hydrogen chloride is stirred for 16 hours at room temperature. The solvent is evaporated under reduced pressure. The residue is heated in ca. 100 mL of water on the steam bath and then cooled in the ice bath, and the precipitate filtered with suction.

Yield: 4.2 g (79% of theoretical yield),

Melting point 103-105 °C

R_f value: 0.33 (silica gel; cyclohexane/ethyl acetate = 2:1)

Example XV

4-(4-[2-(Ethoxycarbonyl)ethyl]phenyl]-2-methylimidazole

A suspension of 5.1 g of 3-[4-(2-chloroacetyl)phenyl]propionic acid ethyl ester, 2.3 g of acetamidine hydrochloride, and 4.7 g of sodium carbonate in 20 mL of anhydrous ethanol is heated for 2 hours to reflux. The solvent is evaporated under reduced pressure and the residue is distributed between ethyl acetate and water. The organic phase is washed three times with water and dried over a magnesium sulfate, and the solvent evaporated under reduced pressure. The residue in chromatographed with cyclohexane/ethyl acetate (3:7) over aluminum oxide, activity grade II.

Yield: 900 mg (17% of theoretical yield)

R_f value: 0.23 (Alox N; ethyl acetate/cyclohexane = 7:3)

Example 1

2-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl)phenyl)-5-[[2-(methoxycarbonyl)ethyl]-aminocarbonyl)-1,3,4-thiadiazole

A solution of 2.0 g of 2-[4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl)phenyl]-5-carboxy-1,3,4-thiadiazole, 1.77 g of 2-[(1H)-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium tetrafluoroborate, 0.72 g of β-alanine methyl ester hydrochloride, 0.75 g of 1-hydroxy-(1H-)benzotriazole, and 1.4 g of N-methylmorpholine in 50 mL of dimethylformamide is stirred for 5 hours at room temperature. The solvent is removed under reduced pressure. Water is added to the residue and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over sodium sulfate, and the solvent is removed under reduced pressure. The crude product is chromatographed with methylene chloride/methanol (9:1) over silica gel, and the product obtained after removal of the solvent is triturated with ethyl acetate and filtered with suction.

Yield: 1.5 g (62% of theoretical yield),

Melting point: 176-178 °C,

R_f value: 0.76 (silica gel; glacial acetate/cyclohexane = 4:1)

Example 2

2-[[2-(Methoxycarbonyl)ethyl]aminocarbonyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

A solution of 1.4 g of 2-[4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl)phenyl]-5-[[2-(methoxycarbonyl)ethyl]aminocarbonyl]-1,3,4-thiadiazole in 40 mL of dioxane and 40 mL of ether saturated with hydrogen chloride is stirred for 2.5 hours at room temperature. The precipitated product is filtered with suction and washed with ether.

Yield: 1.05 g (85% of theoretical yield),

Melting point: 250-255 °C,

Mass spectrum: $M^+ = 374$

R_f value: 0.16 (silica gel; methylene chloride/methanol/conc. ammonia = 9:1:0.1)

The following compounds obtained analogously:

(1) 2-(4-(Methoxycarbonyl)-butyl]-5-(4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

Mass spectrum: $(M + H)^+ = 360$

R_f value: 0.70 (silica gel; methylene chloride/methanol/conc. ammonia = 4 :1:0.25)

(2) 2-[*cis*-4-(Methoxycarbonyl)cyclohexyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

Methanol saturated with hydrogen chloride is added to the reaction solution. After an hour of stirring at room temperature, the solvent is evaporated under reduced pressure.

Mass spectrum: $M^+ = 385$

R_f value: 0.45 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(3) 2-[*trans*-4-(Methoxycarbonyl)cyclohexyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

The reaction is carried out in a 1:1:1 mixture of dioxane, ether saturated with hydrogen chloride, and methanol saturated with hydrogen chloride. After 3 hours of stirring, the precipitated product is filtered with suction and washed with ether.

Mass spectrum: $M^+ = 385$

R_f value: 0.67 (silica gel; methylene chloride/methanol/conc. ammonia = 4 :1:0.25)

(4) 2-[*trans*-4-(Methoxycarbonyl)cyclohexyl]-4-[4-(4-piperidyl)phenyl]imidazole dihydrochloride

(5) 2-[*trans*-4-(Methoxycarbonyl)cyclohexanedehydro-4-piperidyl]phenyl]-1,3-thiazole hydrochloride

(6) 2-[[3-(Methoxycarbonyl)propyl]amino]-4-[4-(4-piperidyl)phenyl]-1,3-thiazole dihydrochloride

(7) 2-[*trans*-4-(Methoxycarbonyl)cyclohexyl]-5-[4-(1-piperazinyl)phenyl]-1,3,4-thiadiazole dihydrochloride

(8) 4-[4-[2-(Ethoxycarbonyl)ethyl]phenyl]-2-[2-(4-piperidyl)ethyl]-1,3-thiazole hydrochloride

(9) 4-[4-[2-(Methoxycarbonyl)ethyl]phenyl]-2-[2-(4-piperidyl)ethyl]imidazole dihydrochloride

(10) 4-[4[2-(Methoxycarbonyl)ethyl]phenyl]-1-methyl-2-[2-(4-piperidyl)ethyl]imidazole dihydrochloride

(11) 4-[4-[2-(Ethoxycarbonyl)ethyl]phenyl]-2-methyl-1-[2-(4-piperidyl)ethyl]imidazole dihydrochloride hydrate

The reaction is performed with ethanol saturated with hydrogen chloride

R_f value: 0.48 (reversed phase; RP8; methanol/5% sodium chloride solution = 6:4)

Calcd. x 1.95 HCl x H_2O:

C, 57.82; H, 7.70; N, 9.15; Cl, 14.95

Found:

C, 57.62; H, 7.68; N, 9.16; Cl, 15.07

(12) 2-[4-[2-(Methoxycarbonyl)ethyl]phenyl]-1-methyl-4-[(3-pyrrolidinyl)oxymethyl]-imidazole dihydrochloride

(13) 4-[4-[2-(Methoxycarbonyl)ethyl]-2-[N-[(4-piperidyl)carbonyl]-N-methylamino]-1,3-thiazole hydrochloride

(14) 2-[4-[2-(Methoxycarbonyl)ethyl]phenyl]-4-[(4-piperidyl)aminocarbonyl]-1,3-thiazole hydrochloride

(15) 2[2-(Methoxycarbonyl)ethyl]-4-[4-[N-[(4-piperidyl)carbonyl]-N-methylamino]-phenyl]-1,3-thiazole hydrochloride

(16) 2-[2-(Methoxycarbonyl)ethyl]-5-[2-[2-(4-piperidyl)ethyl]-5-pyrimidinyl]-1,3,4-thiadiazole hydrochloride

(17) 4-[2-(Methoxycarbonyl)ethyl]-2-[4-[(4-piperidyl)methyloxy]phenyl]-1,3-thiazole dihydrochloride dihydrate

The reaction is carried out in methanol saturated with hydrogen chloride. The precipitate is filtered with suction and washed with *tert*-butyl methyl ether.

Melting point: 95-98 °C

R_f value: 0.28 (reversed phase; RP8; methanol/5% sodium chloride solution = 6:4)

(18) 4-[4-[(Methoxycarbonyl)methyloxy]-phenyl]-2-[4-[(4-piperidyl)ethyl]-1,3-thiazole hydrochloride

Example 3

2-[(2-Carboxyethyl)aminocarbonyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

A suspension of 550 mg of 2-[[2-(methoxycarbonyl)ethyl]aminocarbonyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride in 100 mL of 6N hydrochloric acid is stirred for 3 hours at room temperature. After the addition of another 500 mL of 6N hydrochloric acid, stirring is continued for another hour. The solvent is removed under reduced pressure and the crude product is triturated with a small amount of water and filtered with suction.

Yield: 480 mg (91% the theory),

Mass spectrum: $M^+ = 360$

R_f value: 0.06 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

The following compounds are obtained analogously:

(1) 2-(4-Carboxybutyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-oxadiazole

The crude product and is purified by chromatography.

Mass spectrum: $M^+ = 329$

R_f value: 0.35 (silica gel; methylene chloride/methanol/conc. ammonia = 2:1:0.25)

(2) 2-[*cis*-4-(Carboxycyclohexyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

Melting point: >310 °C

Mass spectrum: $M^+ = 371$

R_f value: 0.17 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(3) 1-[6-(4-Amidinophenyl)-3-pyridazinyl]-4-[2-(n-butanesulfonylamino)-2-carboxyethyl]imidazole hydrochloride

Mass spectrum: $(M + H)^+ = 472$

R_f value: 0.20 (silica gel; methylene chloride/methanol/conc. ammonia = 2:1:0.25)

(4) 4-[4-(2-Carboxyethyl]phenyl]-2-[2-(4-piperidyl)ethyl]-1,3-thiazole

The product of Example 9 is heated in 3N hydrochloric acid for an hour on the steam bath.

Melting point: decomposition starting at 168 °C

R_f value: 0.38 (reversed phase; RP8; methanol/5% sodium chloride solution = 6:4)

(5) 2-(*trans*-4-Carboxycyclohexyl)-4-[4-(4-piperidyl)phenyl]imidazole dihydrochloride

(6) 2-(*trans*-4-Carboxycyclohexyl)-1-methyl-4-[4-(1-methyl-4-piperidyl)phenyl]-imidazole dihydrochloride

(7) 2-(*trans*-4-Carboxycyclohexyl)-1-methyl-4-[4-(4-piperidyl)phenyl]imidazole dihydrochloride

(8) 2-(*trans*-4-Carboxycyclohexyl)-4-[4-(3,4-dehydro-4-piperidyl)phenyl]-1,3-thiazole hydrochloride

(9) 2-[(3-Carboxypropyl)amino]-4-[4-(4-piperidyl)phenyl]-1,3-thiazole dihydrochloride

(10) 2-(*trans*-4-Carboxycyclohexyl)-5-[4-(1-piperazinyl)phenyl]-1,3,4-thiadiazole dihydrochloride

(11) 4-[4-(2-Carboxyethyl)phenyl]-2-[2-(4-piperidyl)ethyl]imidazole dihydrochloride

(12) 4-[4-(2-Carboxyethyl)phenyl]-1-methyl-2-[2-(4-piperidyl)ethyl]imidazole dihydrochloride

(13) 4-[4-(2-Carboxyethyl)phenyl]-2-methyl-1-[2-(4-piperidyl)ethyl]imidazole dihydrochloride hydrate

R_f value: 0.64 (reversed phase; RP8; methanol/5% sodium chloride solution = 6:4)

Calcd. x 1.95 HCl x 0.6 H_2O:

C, 56.77; H, 7.37; N, 9.84; Cl, 16.40

Found:

C, 56.77; H, 7.13; N, 9.93; Cl, 16.34

(14) 2-[4-(2-Carboxyethyl)phenyl]-1-methyl-4-[(3-pyrrolidinyl)oxymethyl]imidazole dihydrochloride

(15) 4-[4-(2-Carboxyethyl)phenyl]-2-FN-[(4-piperidyl)carbonyl]-N-methylamino]-1,3-thiazole hydrochloride

(16) 2-[4-(2-Carboxyethyl)phenyl]-4-[(4-piperidyl)aminocarbonyl]-1,3-thiazole hydrochloride

(17) 2-(2-Carboxyethyl)-4-[4-[N-[(4-piperidyl)carbonyl]-N-methylamino]phenyl]-1,3-thiazole hydrochloride

(18) 2-(2-Carboxyethyl)-5-[2-[2-(4-piperidyl)ethyl]-5-pyrimidinyl]-1,3,4-thiadiazole hydrochloride

(19) 1-[3-(4-Amidinophenyl)-6-pyridazinyl]-3-[2-carboxy-2-(phenylsulfonylamino)-ethyl]indole hydrochloride

(20) 2-(4-Amidinophenyl)-4-[4-[2-(acetylamino)-2-carboxyethyl]phenyl]-5-methyl-1,3-thiazole hydrochloride

(21) 4-(4-Amidinophenyl)-2-[4-[2-(methanesulfonylamino)-2-carboxyethyl]phenyl]-1-methylimidazole hydrochloride

(22) 4-(2-Carboxyethyl)-2-[4-[(4-piperidyl)methyloxy]phenyl]-1,3-thiazole dihydrochloride hydrate

Melting point: decomposition starting at 225 °C

R_f value: 0.36 (reversed phase; RP8; methanol/5% sodium chloride solution = 6:4)

(23) 4-[4-(Carboxymethyloxy)phenyl]-2-(2-(4-piperidyl)ethyl]-1,3-thiazole hydrochloride

(24) 4-[4-(2-Carboxyethyl)phenyl]-2-[2-(4-pyridyl)ethyl]-1,3-thiazole hydrochloride

(25) 4-[4-(2-Carboxyethyl)cyclohexyl]-1-[2-(4-quinuclidinyl)ethyl]-2-methylimidazole dihydrochloride

Example 4

2-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl)phenyl]-5-[4-(methoxycarbonyl)butyl]-1,3,4-thiadiazole

A solution of 2.4 g of N-[4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl]benzoyl]-N'-[[4-(methoxycarbonyl)butyl]carbonyl]hydrazine and 2.1 g of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in 40 mL of tetrahydrofuran is heated for 30 minutes to reflux. The solvent is then evaporated under reduced pressure, and the residue is chromatographed over silica gel.

Yield: 2.4 g (quantitative),

Melting point: 111-113 °C,

Mass spectrum: $M^+ = 459$

R_f value: 0.38 (silica gel; ethyl acetate/cyclohexane = 1:1)

The following compounds are obtained analogously:

(1) 2-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl)phenyl]-5-[*cis*-4-(methoxycarbonyl)-cyclohexyl]-1,3,4-thiadiazole

Melting point: 130-132 °C

Mass spectrum: $M^+ = 485$

R_f value: 0.49 (silica gel; ethyl acetate/cyclohexane = 1:1)

(2) 2-[4-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]phenyl]-5-(*trans*-4-(methoxycarbonyl)-cyclohexyl]-1,3,4-thiadiazole

Melting point 180-182 °C

R_f value: 0.57 (silica gel; cyclohexane/ethyl acetate = 1:1)

(3) 2-[4-[4-(*tert*-Butyloxycarbonyl)-1-piperazinyl]phenyl]-5-[*trans*-4-(methoxycarbonyl)-cyclohexyl]-1,3,4-thiadiazole

Example 5

2-(4-Carboxybutyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

A solution of 1.0 g of 2-[4-(methoxycarbonyl)butyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride and 0.22 g of lithium hydroxide hydrate in 30 mL of tetrahydrofuran and 24 mL of water is stirred for 60 minutes at room temperature. The reaction solution is acidified with 1N hydrochloric acid. Excess tetrahydrofuran is evaporated under reduced pressure, and the precipitate is filtered with suction and washed with a small amount of water.

Yield: 0.80 g (83% of theoretical yield),

Mass spectrum: $M^+ = 345$

R_f value: 0.18 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

The following compounds are obtained analogously:

(1) 3-(4-Carboxycyclohexyl]-4-phenyl-5-[4-(4-piperidyl)phenyl]-1,2,4-triazole

After the acidification, the solvent mixture is evaporated under reduced pressure, and the crude product is chromatographed over silica gel.

Mass spectrum: $M^+ = 430$

R_f value: 0.12 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(2) 3-(4-Carboxybutyl)-4-phenyl-5-[4-(4-piperidyl)phenyl]-1,2,4-triazole

After the acidification, the solvent mixture is evaporated under reduced pressure, and the crude product is chromatographed over silica gel.

Mass spectrum: $M^+ = 404$

R_f value: 0.24 (silica gel; methylene chloride/methanol/conc. ammonia = 2:1:0.25)

(3) 2-(*trans*-4-Carboxycyclohexyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride Mass spectrum: $M^+ = 371$

R_f value: 0.09 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(4) 2-(4-Carboxycyclohexyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-oxadiazole

After the acidification, the solvent mixture is evaporated under reduced pressure, and the crude product is chromatographed over silica gel.

Mass spectrum: $M^+ = 355$

R_f value: 0.09 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

(5) 2-(*trans*-4-Carboxycyclohexyl)-5-[4-(2,2,6,6-tetramethyl-4-piperidyl)phenyl]-1,3,4-thiazole hydrochloride

(6) 2-(*trans*-4-Carboxycyclohexyl)-4-[4-(4-cyano-4-piperidyl)phenyl]-1-methylimidazole dihydrochloride

Example 6

2-[4-(Methoxycarbonyl)butyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-oxadiazole

A solution of 2.0 g of N-[4-[1-(*tert*-butyloxycarbonyl)-4-piperidyl]benzoyl]-N'-[[4-(methoxycarbonyl)butyl]carbonyl]hydrazine and 0.3 mL of pyridine in 18 mL of thionyl chloride is stirred for 3 hours at room temperature. Next, the mixture is heated to reflux for 45 minutes. Excess thionyl chloride is evaporated under reduced pressure, the residue combined with toluene, and the solvent again evaporated under reduced pressure. The residue is chromatographed over silica gel.

Yield: 0.24 g (15% of theoretical yield),

Mass spectrum: $M^+ = 343$

R_f value: 0.16 (silica gel; methylene chloride/methanol/conc. ammonia = 8:1:0.1)

The following compound is obtained analogously:

(1) 2-[4-(Methoxycarbonyl)cyclohexyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-oxadiazole

Mass spectrum: $M^+ = 369$

R_f value: 0.24 (silica gel; methylene chloride/methanol/conc. ammonia = 9:1)

Example 7

3-[4-(Methoxycarbonyl)cyclohexyl]-4-phenyl-5-[4-(4-piperidyl)phenyl]-1,2,4-triazole

220 mg of phosphorus trichloride is added to a solution of 785 mg of aniline in 5 mL of 1,2-dichlorobenzene, and the mixture is heated for a short time to 60 °C. Next, 700 mg of N-[4-[4-(*tert*-butyloxycarbonyl)-4-piperidine]benzoyl]-N'-[[*cis*-4-(methoxycarbonyl)cyclohexyl]-carbonyl]hydrazine is added and the mixture is heated for 2.5 hours to reflux. The solvent is evaporated under reduced pressure. Water and sufficient 1 N sodium hydroxide solution to make the solution alkaline are added to the residue. The aqueous phase is extracted once with methylene chloride and once with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is evaporated under reduced pressure. The residue is chromatographed over silica gel.

Yield: 550 mg (86% of theoretical yield),

Mass spectrum: $(M + H)^+ = 445$

R_f value: 0.36 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

The following compound is obtained analogously:

(1) 3-[4-(Methoxycarbonyl)butyl]-4-phenyl-5-[4-(4-piperidyl)phenyl]-1,2,4-triazole

R_f value: 0.34 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Example 8

1-[6-(4-Amidinophenyl)-3-pyridazinyl]-4-[2-(n-butanesulfonylamino)-2-(methoxycarbonyl)ethyl]imidazole

Hydrogen chloride is passed through a solution of 700 mg of 4-[2-(n-butanesulfonylamino)-2-(methoxycarbonyl)ethyl]-1-[6-(4-cyanophenyl)-3-pyridazinyl]imidazole in 250 mL of

anhydrous methanol for an hour at 0 °C with stirring. After 16 hours of stirring at room temperature, the solvent is evaporated under reduced pressure at a bath temperature of 30 °C. The residue is dissolved in 50 mL of anhydrous methanol and after addition of 3 g of ammonium carbonate stirred for 4 hours at room temperature. The precipitate is filtered with suction and rewashed with anhydrous methanol. The filtrate is concentrated by evaporation under reduced pressure and the residue is chromatographed over silica gel.

Yield: 250 mg (34% of theoretical yield),

Melting point: 227-229 °C

Mass spectrum: $(M + H)^+ = 486$

R_f value: 0.09 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

The following compounds are obtained analogously:

(1) 1-[3-[4-Amidinophenyl]-6-pyridazinyl]-3-[2-(methoxycarbonyl)-2-(phenylsulfonylamino)ethyl]indole

(2) 4-[4-[2-(Acetylamino)-2-(methoxycarbonyl)ethyl]phenyl]-2-(4-amidinophenyl)-5-methyl-1,3-thiazole

(3) 4-[4-Amidinophenyl)-1-methyl-2-[4-[2-(methanesulfonylamino)-2-(methoxycarbonyl)ethyl]phenyl]imidazole

Example 9

2-[2-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]ethyl]-4-[4-[2-(ethoxycarbonyl)ethyl]phenyl]-1,3-thiazole

A solution of 550 mg of 1-(*tert*-butyloxycarbonyl)-4-(2-thioamidoethyl)piperidine and 530 mg of 3-[4-(2-chloroacetyl)phenyl]propionic acid ethyl ester in 30 mL of methanol is heated for 14 hours to reflux. Next, 500 mg of ethyldiisopropylamine and a solution of 500 mg of dicarboxylic di-*tert*-butylester in ether are added dropwise at room temperature. The mixture is stirred for 10 minutes at room temperature and the solvent is removed under reduced pressure. The residue is chromatographed over silica gel.

Yield: 300 mg (32% of theoretical yield),

R_f value: 0.26 (silica gel; cyclohexane/ethyl acetate = 8:2)

Example 10

2-[4-[[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]methyloxy]phenyl]-4-[2-(methoxycarbonyl)ethyl]-1,3-thiazole

1.7 g of potassium-*tert*-butylate is added to a solution of 4.09 g of 2-(4-hydroxyphenyl)-4-[2-(methoxycarbonylethyl]-1,3-thiazole in 1000 mL of anhydrous dimethylformamide, and the mixture is stirred for 15 minutes at room temperature. 4.5 g of 1-(*tert*-butyloxycarbonyl)-4-(mesyloxymethyl)piperidine is added and the mixture is heated for 24 hours to 60 °C. After addition of another 0.9 g of potassium-*tert*-butylate and 2.2 g of 1-(*tert*-butyloxycarbonyl)-4-(mesyloxymethyl)piperidine is stirred further for 2 days at 60 °C. The solvent is evaporated under reduced pressure and the remaining residue is chromatographed over silica gel.

Yield: 4.3 (68% of theoretical yield),

Melting point: 75-77 °C

R_f value: 0.70 (silica gel; methylene chloride/ethyl acetate = 4:1)

Example 11

1-[2-[1-(*tert*-Butyloxycarbonyl)-4-piperidyl]ethyl]-4-[4-[2-(ethoxycarbonyl)ethyl]phenyl]-2-methylimidazole

A suspension of 820 mg of 4-[4-[2-(ethoxycarbonyl)ethyl]phenyl]-2-methylimidazole and 140 mg of 55% sodium hydride in mineral oil in 5 mL of dimethylformamide is stirred for 30 minutes at room temperature. 980 mg of 1-(*tert*-butyloxycarbonyl)-4-[2-(methanesulfonyloxy)-ethyl]piperidine is added and the mixture is stirred for 2 hours at room temperature. The solvent is evaporated under reduced pressure and the residue is distributed between water and ethyl acetate. After the aqueous phase is neutralized with 2N citric acid, the aqueous phase is repeatedly extracted with ethyl acetate. The combined ethyl acetate phases are washed with water and dried over a magnesium sulfate, and the solvent evaporated under reduced pressure. The residue is chromatographed with cyclohexane/ethyl acetate (1:1) over aluminum oxide, activity grade III.

Yield: 650 mg (43% of theoretical yield),

R_f value: 0.29 (aluminum oxide N; cyclohexane/ethyl acetate = 1:1)

Example 12

2-[*trans*-4-(Isopropyloxycarbonyl)cyclohexyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride

A suspension of 200 mg of 2-(*trans*-4-carboxycyclohexane)-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole hydrochloride in 650 mL of anhydrous isopropanol, saturated with hydrogen chloride, is stirred for 24 hours at room temperature. The solvent is evaporated under reduced pressure. The residue is triturated with a small amount of isopropanol and filtered with suction.

Yield: 180 mg (82% of theoretical yield),

Melting point: 295-300 °C (dec.)

R_f value: 0.67 (silica gel; methylene chloride/methanol/conc. ammonia = 4:1:0.25)

Example 13

Dry ampoule containing 2.5 mg of active substance per 1 mL

Composition

Active substance	2.5 mg
Mannitol	50.0 mg
Water for injection	to 1.0 mL

Preparation:

The active substance and mannitol are dissolved in water. After filling, the ampoule is freeze-dried. The dissolution to obtain a ready-to-use solution is carried out with water for injection.

Example 14

Dry ampoule containing 35 mg of active substance per 2 mL

Composition

Active substance	35.0 mg
Mannitol	100.0 mg
Water for injection	to 2.0 mL

Preparation

The active substance and mannitol are dissolved in water. After filling, the ampoule is freeze-dried. The dissolution to obtain a ready-to-use solution is carried out with water for injection.

Example 15

Tablets containing 50 mg of active substance

Composition

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Corn starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation

(1), (2), and (3) are mixed and granulated with an aqueous solution of (4). (5) is added to the dry granules. From this mixture, tablets are pressed which are biplanar with an edge on both sides and a breaking notch on one side. Diameter of the tablets: 9 mm.

Example 16

Tablets containing 350 mg of active substance

Composition

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Corn starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation

(1), (2), and (3) are mixed and granulated with an aqueous solution of (4). (5) is added to the dry granules. From this mixture, tablets are pressed which are biplanar with an edge on both sides and a breaking notch on one side.

Diameter of the tablets: 12 mm.

Example 17

Capsules containing 50 mg of active substance

Composition

(1) Active substance	50.0 mg
(2) Corn starch dried	58.0 mg
(3) Lactose pulverized	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is filled into hard gelatin capsules, size 3, on a capsule filling machine.

Example 18

Capsules containing 350 mg of active substance

Composition

(1) Active substance	350.0 mg
(2) Corn starch dried	46.0 mg
(3) Lactose pulverized	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

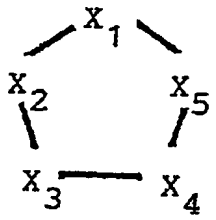
Preparation

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is filled into hard gelatin capsules, size 0, on a capsule filling machine.

Claims

1. 5-membered heterocycles of the general formula



(I)

in which

(i) with the proviso that the 5-membered heterocyclic ring is not a pyrrolidine, pyrroline, pyrrolinone, or pyrrolidinone ring and contains at least one carbon atom and

(ii) with the exception of the compounds of 3-(4-amidinophenyl)-1-[4-(2-amino-2-carboxyethyl)phenyl]-2H-pyrazol-5-one and 3-(4-amidinophenyl)-1-[4-(2-amino-2-methoxycarbonylethyl)phenyl]-2H-pyrazol-5-one,

one of the radicals X_1 to X_5 is a group of the formulas

A – B – C – N< ,
A – B – C – CH< or
A – B – C – C⁄ , in which

A is a cycloalkyl group having 5 to 7 carbon atoms, which is optionally substituted by 1 to 4 alkyl groups or by a hydroxy, alkoxy, phenylalkoxy, cyano, aminocarbonyl, carboxy, alkoxycarbonyl, or phenylalkoxycarbonyl group, and in which an unsubstituted methylene group is replaced by the R_a-N< group, whereby

R_a is a hydrogen atom, an alkyl group, an alkoxycarbonyl group having a total of 2 to 6 carbon atoms, a phenylalkoxycarbonyl group, an alkenyloxycarbonyl group having a total 4 to 6 carbon atoms, a cycloalkoxycarbonyl group having a total 6 to 8 carbon atoms, or an

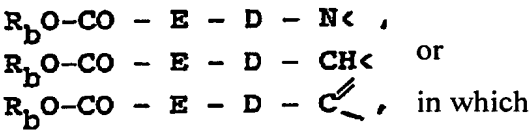
R_1-CO-O-(R_2CH)-O-CO- group,

in which

R_1 is an alkyl group having 1 to 5 carbon atoms, a cycloalkyl group having 5 to 7 carbon atoms, a phenylalkyl group, an alkoxy group having 1 to 5 carbon atoms, a cycloalkoxy group having 5 to 7 carbon atoms, or a phenyl group, and

R_2 is a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, a cycloalkyl group having 5 to 7 carbon atoms, or a phenyl group,
and additionally in the 6- or 7-membered azacycloalkyl groups thus formed a >CH- unit in the 4-position can be replaced by a nitrogen atom or in the 5- to 7-membered azacycloalkyl groups thus formed, a $-CH_2-CH<$ unit by a $-CH=C<$ unit, and in the piperazinyl or homopiperazinyl rings thus formed, a methylene group, which is adjacent to the nitrogen atom in the 4-position, by a carbonyl group,
a pyridyl or quinuclidinyl group or also, if
D is an alkylene or alkenylene group, each having up to 8 carbon atoms, which is substituted by an $R_3R_4N-CO-NR_5-$ or $R_6-SO_2-NR_3-$ group, in which
R_3 to R_5, which may be identical or different, each is a hydrogen atom or an alkyl or phenylalkyl group, and
R_6 is an alkyl group having 1 to 5 carbon atoms or a phenylalkyl or phenyl group,
or E is straight-chain or branched alkylene or alkenylene group, each having up to 5 carbon atoms, which is substituted by a hydroxy, alkoxy, alkylsulfenyl, R_3R_4N-, R_3O-CO-, R_6CO-NR_3-, $R_6O-CO-NR_3-$, $R_6SO_2-NR_3-$, or $R_3R_4N-CO-NR_5-$ group, in which R_3 to R_6 are defined as mentioned above,
a phenyl group, which is substituted in the 4-position by an R_aNH-CH_2- or $R_aNH-C(=NH)-$ group, or a phenyl group, to which an n-alkylene bridge having 3 or 4 carbon atoms, which is substituted by an R_aNH group, is attached via two adjacent carbon atoms, whereby R_a is defined in each case as mentioned above,
B is a bond, an alkyl group or an $-OCH_2-$, $-CH_2O-$, $-SCH_2-$, $-CH_2S-$, $-CONR_3-$, $-R_3NCO-$, $-CH_2NR_3-$, $-NR_3CH_2-$, $-SO_2NR_3-$, or $-NR_3SO_2-$ group, whereby R_3 is defined as mentioned above and an oxygen or nitrogen atom of the radical B is not bonded directly to a nitrogen atom of the radical A or the 5-membered heterocycle,
C is a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms, or by alkyl, trifluoromethyl, hydroxy, alkoxy, alkylsulfenyl, alkylsulfinyl, or alkylsulfonyl groups, whereby the substituents may be identical or different,
a pyridinylene, pyrimidinylene, pyrazinylene, or pyridazinylene group, each of which can be substituted in the carbon skeleton by a chlorine atom or by an alkyl or alkoxy group,
a 1,4-cyclohexylene, 1,3-piperidinylene, 1,4-piperidinylene, or 1,4-piperazinylene group or also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas



or

or

in which

D is a -CO-NR_3-, -NR_3-CO-, -SO_2-NR_3-, or -NR_3-SO_2- group, a straight-chain or branched alkylene or alkenylene group, which is optionally substituted by a hydroxy, alkoxy, alkylsulfenyl, R_3R_4N-, R_3O-CO-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or R_3R_4N-CO-NR_5- group, and in which in each case the alkylene moiety can contain 1 to 8 carbon atoms and the alkenylene moiety 2 to 8 carbon atoms, and R_3 to R_6 are defined as mentioned above,

a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms, or by alkyl, trifluoromethyl, hydroxy, alkoxy, alkylsulfenyl, alkylsulfinyl, or alkylsulfonyl groups,

a pyridinylene, pyrimidinylene, pyrazinylene, pyridazinylene, or triazenylene group, each of which can be substituted in the carbon skeleton by a chlorine atom or by an alkyl or alkoxy group, whereby additionally one or two -CH=N- groups each can be replaced by a -CO-NR_3- group, in which R_3 is defined as mentioned above, and then one of the nitrogen atoms can also be bonded to the radical E, instead of to the radical R_3, if E is not a bond and is not bonded via an oxygen or sulfur atom to the radical D, or to the atom, in the ring, of the respective radical X_1 to X_5,

a cycloalkylene group having 4 to 5 carbon atoms, which is optionally substituted by an alkyl, phenylalkyl, or phenyl group and in which a >CH- unit can be replaced by a nitrogen atom and additionally a methylene group, adjacent to the nitrogen atom, by a carbonyl group,

a cycloalkylene group having 6 or 7 carbon atoms, which is optionally substituted by an alkyl, phenylalkyl, or phenyl group and in which one or two >CH- units can each be replaced by a nitrogen atom, whereby additionally in each case one or two methylene groups, adjacent to a nitrogen atom, can be replaced by a carbonyl group, or

an alkylene group having 1 to 5 carbon atoms, which is linked via the radical W_1 to the atom, in the ring, of the respective radical X_1 to X_5 and in which W_1 is an NR_3 group, in which R_3 is defined as mentioned above, or an oxygen or sulfur atom, whereby an oxygen or sulfur atom of the radical W_1 may not be bonded directly to a nitrogen atom of the 5-membered heterocycle,

E is a bond,

a straight-chain or branched alkylene or alkenylene group, which is optionally substituted by a hydroxy, alkoxy, alkylsulfenyl, R_3R_4N-, R_3O-CO-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or

R_3R_4N-CO-NR_5- group and in which in each case the alkylene moiety can contain 1 to 5 carbon atoms and the alkenylene moiety 2 to 5 carbon atoms, and R_3 to R_6 are defined as mentioned above, or

an alkylene group, which is linked via the radical W_2 to the radical D and in which W_2 is an oxygen or sulfur atom, a sulfinyl, sulfonyl, -NR_3-, -(R_6CO)N-, -(R_6SO_2)N-, -$CONR_3$-, or -NR_3CO- group, in which R_3 and R_6 are defined as mentioned above, and whereby an oxygen or sulfur atom of the radical W_2 is not bonded directly to a nitrogen atom of the radical D, and

R_b is a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, or an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are defined as mentioned above,

a third of the radicals X_1 to X_5 is a sulfur atom,

HN<, R_6N<, R_7C< or (R_7)$_2$C< group

or a N atom, whereby R_6 is as defined at the outset and R_7 is a hydrogen atom, an alkyl, phenylalkyl, phenyl, alkoxy, R_3R_4N-, R_3O-CO-, or R_3R_4N-CO group, whereby R_3 and R_4 are defined as mentioned above,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or an

R_7C< group,

in which R_7 is defined as mentioned above, or is also a carbonyl group, when it is not located between two nitrogen atoms,

a fifth of the radicals X_1 to X_5 is a nitrogen atom, an

R_7C< or (R_7)$_2$C<- group,

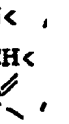
whereby R_7 is defined as mentioned above,

or also two adjacent radicals of the radicals X_1 to X_3 together are an o-phenylene group, whereby, if it was not specified otherwise,

the aforementioned alkyl, alkylene, or alkoxy moieties each can contain 1 to 3 carbon atoms, tautomers thereof, stereoisomers thereof, including mixtures and salts thereof.

2. 5-membered heterocycles of the general formula I according to claim 1, in which

one of the radicals X_1 to X_5 is a group of the formulas



or

in which

A is a cycloalkyl group having 5 to 7 carbon atoms, which is optionally substituted by 1 to 4 alkyl groups or by a hydroxyl, alkoxy, cyano, aminocarbonyl, carboxyl, or alkoxycarbonyl group, and in which an unsubstituted methylene group is replaced by the R_a-N< group, whereby

R_a is a hydrogen atom, an alkyl group, an alkoxycarbonyl group having a total of 2 to 6 carbon atoms, a phenylalkoxycarbonyl group, a cycloalkoxycarbonyl group having a total 6 to 8 carbon atoms, or an

R_1-CO-O-(R_2CH)-O-CO- group,

in which

R_1 is an alkyl group, a cycloalkyl group having 5 to 7 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a cycloalkoxy group having 5 to 7 carbon atoms, or a phenyl group, and

R_2 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms,

and additionally in the 6- or 7-membered azacycloalkyl groups thus formed, a >CH- unit in the 4-position can be replaced by a nitrogen atom or in the 5- to 7-membered azacycloalkyl groups thus formed, a -CH_2-CH< unit by a -CH=C< unit

a pyridyl or quinuclidinyl group or also, if

D is an alkylene group having 1 to 5 carbon atoms, which is substituted by an R_3R_4N-CO-NR_5- or R_6-SO_2-NR_3- group, in which

R_3 to R_5, which may be identical or different, each is a hydrogen atom or an alkyl or phenylalkyl group, and

R_6 is an alkyl group having 1 to 5 carbon atoms or a phenylalkyl or phenyl group,

or E is a straight-chain or branched alkylene group each having 1 to 5 carbon atoms, which is substituted by an R_3R_4N-, R_6CO-NR_3-, R_6SO_2-NR_3-, R_3R_4N-CO-NR_5-, hydroxy, or alkoxy group, in which R_3 to R_6 are defined as mentioned above,

a phenyl group, which is substituted in the 4-position by an R_aNH-CH_2- or R_aNH-C(=NH)- group, or a phenyl group, to which an n-propylene or n-butylene bridge is attached via positions 3 and 4, whereby the n-propylene- and n-butylene bridge is substituted by an R_aNH- group and R_a in each case is defined as mentioned above,

B is a bond, a $-CH_2-CH_2-$, $-OCH_2-$, $-CH_2O-$, $-CONR_3-$, or $-R_3NCO-$ group, whereby R_3 is defined as mentioned above and an oxygen or nitrogen atom of the radical B is not bonded directly to a nitrogen atom of the radical A or the 5-membered heterocycle,

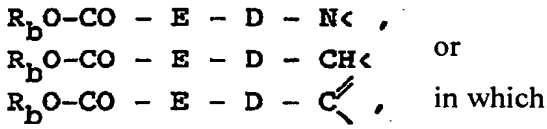
C is a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms, or by alkyl, trifluoromethyl, hydroxy, or alkoxy groups, whereby the substituents may be identical or different,

a pyridinylene, pyrimidinylene, pyrazinylene, or pyridazinylene group, each of which can be substituted in the carbon skeleton by an alkyl or alkoxy group,

a 1,4-cyclohexylene, 1,4-piperidinylene, or 1,4-piperazinylene group, or

also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas



or

or

in which

D is a $-CO-NR_3-$ or $-NR_3-CO-$ group, a straight-chain or branched alkylene or alkenylene group which is optionally substituted by a hydroxy, alkoxy, R_3R_4N-, R_6CO-NR_3-, $R_6O-CO-NR_3-$, $R_6SO_2-NR_3-$, or $R_3R_4N-CO-NR_5-$ group, and in which in each case the alkylene moiety can contain 1 to 5 carbon atoms and the alkenylene moiety 2 to 5 carbon atoms, and R_3 to R_6 are defined as mentioned above,

a phenylene group, which can be mono- or disubstituted by fluorine, chlorine, or bromine atoms, by alkyl, trifluoromethyl, hydroxy, or alkoxy groups,

a pyridinylene, pyrimidinylene, pyrazinylene, or pyridazinylene group, each of which can be substituted in the carbon skeleton by an alkyl or alkoxy group,

a cyclohexylene group, in which one or two >CH- units can each be replaced by a nitrogen atom, whereby additionally a methylene group, adjacent to a nitrogen atom, can be replaced by a carbonyl group, or

an alkylene group having 1 to 4 carbon atoms, which is linked via the radical W_1 to the atom, in the ring, of the respective radical X_1 to X_5 and in which W_1 is an NR_3 group, in which R_3 is defined as mentioned above, or an oxygen or sulfur atom, whereby an oxygen or sulfur atom of the radical W_1 may not be bonded directly to a nitrogen atom of the 5-membered heterocycle,

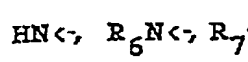
E is a bond,

a straight-chain or branched alkylene group having 1 to 5 carbon atoms, which is optionally substituted by a hydroxy, alkoxy, R_3R_4N-, R_6CO-NR_3-, R_6O-CO-NR_3-, R_6SO_2-NR_3-, or R_3R_4N-CO- NR_5- group, whereby R_3 to R_6 are defined as mentioned above, or

an alkylene group, which is linked via the radical W_2 to the radical D, and in which W_2 is an oxygen or sulfur atom, or an -NR_3-, -$(R_6CO)N$-, or -$(R_6SO_2)N$- group, in which R_3 and R_6 are defined as above, and whereby an oxygen or sulfur atom of the radical W_2 is not bonded directly to a nitrogen atom of the radical D, and

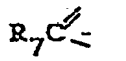
R_b is a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl group having 5 to 7 carbon atoms, or an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are defined as mentioned above,

a third of the radicals X_1 to X_5 is an

 or an $(R_7)_2C<$ group

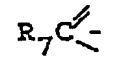
or a N atom, whereby R_6 is as defined at the outset and R_7 is a hydrogen atom or an alkyl or phenyl group,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or an

 group,

in which R_7 is defined as mentioned above,

a fifth of the radicals X_1 to X_5 is a nitrogen atom or an

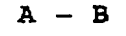
 or an $(R_7)_2C<$ group,

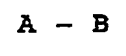
whereby R_7 is defined as mentioned above,

or also two adjacent radicals of the radicals X_1 to X_5 together are an o-phenylene group,

tautomers thereof, stereoisomers thereof, including mixtures and salts thereof.

3. 5-membered heterocycles of the general formula I according to claim 1, in which one of the radicals X_1 to X_5 is a group of the formulas

 or

 , in which

A is a 1,3-pyrrolidinyl, 1,3-piperidyl, or 1,4-piperidyl group, optionally substituted in the carbon skeleton by 1 to 4 methyl groups or by a hydroxy, methoxy, cyano, or aminocarbonyl group, whereby the aforementioned azabicycles are substituted in the 1-position by the radical R_a and

R_a is a hydrogen atom, a methyl group, an ethyl group, or an alkoxycarbonyl group having a total of 2 to 6 carbon atoms,

a 1,4-piperazinyl or 3,4-dehydro-1,4-piperidyl group, each of which is substituted in the 1-position by the radical R_a and R_a is defined as mentioned above,

a pyridyl or quinuclidinyl group or also, if

D is an ethylene group substituted by an R_6-SO_2-NR_3- group, in which

R_3 is a hydrogen atom, a methyl or ethyl group, and

R_6 is an alkyl group having 1 to 5 carbon atoms or a phenyl group,

or E is an ethylene group, which is substituted by an amino, R_6CO-NR_3-, R_6SO_2-NR_3-, or hydroxy group, in which R_3 and R_6 are defined as mentioned above, and

R_4 and R_5, which may be identical or different, each is a hydrogen atom or a methyl or ethyl group,

a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group,

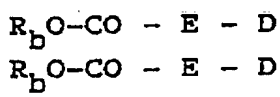
B is a bond, a -CH_2-CH_2-, -OCH_2-, -CH_2O-, -$CONR_3$-, or -R_3NCO- group, whereby R_3 is defined as mentioned above and an oxygen or nitrogen atom of the radical B is not bonded directly to a nitrogen atom of the radical A or the 5-membered heterocycle,

C is a phenylene group, which can be substituted by a chlorine atom or by a methyl group,

a pyridinylene, pyrimidinylene, or pyridazinylene group, or

also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas



or

, in which

D is a -CO-NR_3- or -NR_3-CO- group, whereby R_3 is defined as mentioned above, or a straight-chain or branched alkylene group having 1 to 5 carbon atoms,

a phenylene group, which may be substituted by a chlorine atom or a methyl group,

a 1,4-cyclohexylene group, or

an alkylene group having 1 to 4 carbon atoms, which is linked via an -NR_3- group, whereby R_3 is defined as mentioned above, to the atom, in the ring, of the respective radical X_1 to X_5,

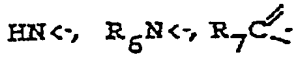
E is a bond,

an ethylene group optionally substituted by an R_6CO-NR_3- or R_6SO_2-NR_3- group, whereby R_3 and R_6 are defined as mentioned above, or

an -O-CH_2- or -NR_3-CH_2- group, whereby R_3 is defined as mentioned above, and

R_b is a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, or a cycloalkyl group having 5 or 6 carbon atoms,

a third of the radicals X_1 to X_5 is an

 group

or a N atom, whereby R_6 is defined as mentioned above and R_7 is a hydrogen atom or a methyl or ethyl group,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or an

 group,

in which R_7 is defined as mentioned above,

a fifth of the radicals X_1 to X_5 is a nitrogen atom or an

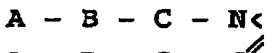
 group,

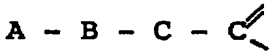
whereby R_7 is defined as mentioned above,

or also two adjacent radicals of the radicals X_1 to X_5 together are an o-phenylene group,

tautomers thereof, stereoisomers thereof, including mixtures and salts thereof.

4. 5-membered heterocycles of the general formula I according to claim 1, in which one of the radicals X_1 to X_5 is a group of the formulas

 or

 , in which

A is a 4-piperidyl group substituted in the 1-position by the radical R_a, whereby

R_a is a hydrogen atom or an alkoxycarbonyl group having a total of 2 to 6 carbon atoms,

or also, if

D is an ethylene group substituted by an R_6-SO_2-NR_3- group, in which

R_3 is a hydrogen atom and

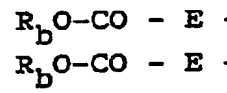
R_6 is an alkyl group having 1 to 5 carbon atoms,

a phenyl group, which is substituted in the 4-position by an NH_2-C(=NH)- group,

B is a bond or a -CH_2-CH_2- or -CH_2O- group,

C is a phenylene group or also a bond, if B is not a bond,

a second of the radicals X_1 to X_5 is a group of the formulas

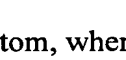

, in which

D is a -CO-NH-group, an alkylene group having 1 to 5 carbon atoms, a phenylene group, or a 1,4-cyclohexylene group,

E is a bond or an ethylene group, and

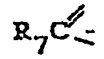
R_b is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms,

a third of the radicals X_1 to X_5 is an $R_6N<$

$R_6N<$- or[sic]  group,

or a N atom, whereby R_6 is a phenyl group and R_7 a hydrogen atom or a methyl or ethyl group,

a fourth of the radicals X_1 to X_5 is an oxygen, sulfur, or nitrogen atom, or a

 group,

in which R_7 is defined as mentioned above,

a fifth of the radicals X_1 to X_5 is a nitrogen atom,

tautomers thereof, stereoisomers thereof, including mixtures and salts thereof.

5. The following compounds of the general formula I according to claim 1:

(i) 2-(*trans*-4-carboxycyclohexyl)-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole,

(ii) 2-[*trans*-4-(methoxycarbonyl)cyclohexyl]-5-[4-(4-piperidyl)phenyl]-1,3,4-thiadiazole,

(iii) 1-[6-(4-amidinophenyl)-3-pyridazinyl]-4-[2-(n-butanesulfonylamino)-2-carboxy-ethyl]imidazole, and

(iv) 1-[6-(4-amidinophenyl)-3-pyridazinyl]-4-[2-(n-butanesulfonylamino)-2-(methoxycarbonyl)ethyl]imidazole,

and the salts thereof.

6. Physiologically tolerable addition salts of the compounds of at least one of the claims 1 through 5 with inorganic or organic acids or bases.

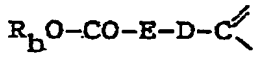
7. Medicaments containing a compound according to at least one of the claims 1 through 5 or a physiologically tolerable addition salt according to claim 6, in addition to optionally one or more inert vehicles and/or diluents.

8. Use of a compound according to at least one of the claims 1 through 6 for the preparation of a medicament, which is suitable for the control or prevention of diseases, in which relatively small or relatively large cell aggregates occur or cell-matrix interactions play a part.

9. Process for the preparation of a medicament according to claim 7, characterized in that a compound according to at least one of claims 1 through 6 is incorporated in a nonchemical manner into one or more inert vehicles and/or diluents.

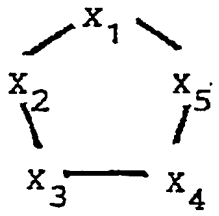
10. Processes for the preparation of 5-membered heterocycles according to claims 1 through 7, characterized in that

a) to prepare compounds of the general formula I, in which one of second of the radicals X_1 to X_5 is an R_bO-CO-E-D-CH<- or



group,

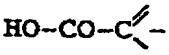
a compound of the general formula



(II)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that a second of the radicals X_1 to X_5 is an HO-CO-CH<- or



group,

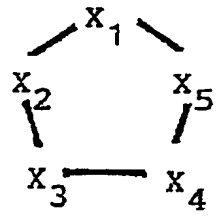
or the reactive derivatives thereof is reacted with a compound of the general formula

$R_bO - CO - E - HNR_3$ (III)

in which

R_3, R_b, and E are defined as in claims 1 through 5, or

b) to prepare compounds of the general formula I, in which R_a is a hydrogen atom, a protective group of a compound of the general formula

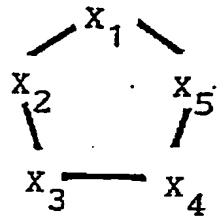


(IV)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that R_a is an alkoxycarbonyl group having a total of 2 to 6 carbon atoms, a phenylalkoxycarbonyl group, an alkenyloxycarbonyl group having a total 4 to 6 carbon atoms, a cycloalkoxycarbonyl group having a total 6 to 8 carbon atoms, or a removable protective group for an imino group, is removed by means of hydrolysis, hydrogenolysis, or thermolysis, or

c) to prepare compounds of the general formula I, in which R_b is a hydrogen atom, a protective group of a compound of the general formula

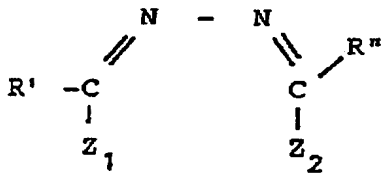


(V)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that R_b is an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety, or a removable protective group for a carboxy group is removed by means of hydrolysis, hydrogenolysis, or thermolysis, or

d) to prepare 1,3,4-oxadiazole, 1,2,4-triazole, and 1,3,4-thiadiazole derivatives of the general formula I, a compound optionally formed in the reaction mixture of the general formula

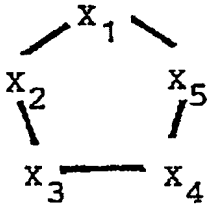


(VI)

in which

Z_1 and Z_2, which may be identical or different, are halogen atoms, amino groups optionally substituted by R_6, hydroxy, alkoxy, mercapto, or alkylmercapto groups, one of the radicals R' or R" is an A-B-C-group and the other of the radicals R' or R" an R_bO-CO-E-D group, is cyclized and, if necessary, a thus obtained compound is alkylated, or

e) to prepare compounds of the general formula I, in which A is a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group, a compound, optionally formed in the reaction mixture, of the general formula



(VII)

in which

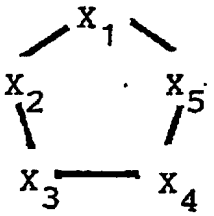
X_1 to X_5 are as defined in claims 1 through 5, with the proviso that A is a phenyl group, which is substituted in the 4-position by a Z_3-C(=NH)- group, whereby Z_3 is an alkoxy, aralkoxy, alkylthio, aralkylthio, or amino group, is reacted with an amine of the general formula

R_a'-NH_2 (VIII)

in which

R_a' is a hydrogen atom or an alkyl group having 1 to 3 carbon atoms, or

f) to prepare compounds of the general formula I, in which A is a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group, a compound of the general formula

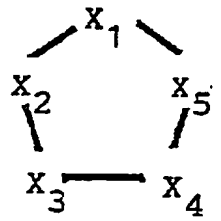


(IX)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that A is a phenyl group, which is substituted in the 4-position by a cyano group, is reacted with hydroxylamine and the thus obtained amidoxime is then reduced, or

g) to prepare compounds of the general formula I, in which A is a phenyl group, which is substituted in the 4-position by an R_aNH-C(=NH)- group, a compound of the general formula



(IX)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that A is a phenyl group, which is substituted in the 4-position by a cyano group, is reacted with an appropriate alkylchloroaluminum amide, or

h) to prepare 1,3-thiazoles and imidazoles of the general formula I, a compound of the general formula

R'-CO-CH_2-Z_4 (X)

is reacted with a compound of the general formula

R''-CU-NH_2 (XI)

in which

one of the radicals R' or R" is an A-B-C group and the other of the radicals R' or R" an R_bO-CO-E-D group,

Z_4 is a nucleophilic leaving group, and

U is a sulfur atom or an imino group, or

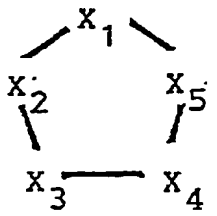
i) to prepare compounds of the general formula I, in which R_a, with exception the hydrogen atom, is as defined at the outset and B is a -CH_2O- group, a compound of the general formula

A-CH_2-Z_5 (XII)

in which

A is as defined in claims 1 through 5, with the proviso that R_a, with exception the hydrogen atom, is as defined in claims 1 through 5, and

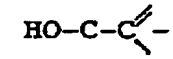
Z_5 is a nucleophilic leaving group is reacted with a compound of the general formula



(XIII)

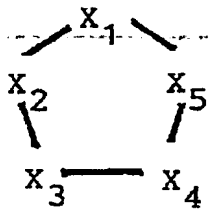
in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that a second of the radicals X_1 to X_5 is an

HO-C-CH< or  group,

whereby C is as defined in claims 1 through 5, or with the alkali or alkaline earth metal salts thereof, or

j) to prepare compounds of the general formula I, in which one of the radicals X_1 to X_5 is an A-B-C-N< or R_bO-CO-E-D-N< group,
a compound of the general formula



(XIV)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that one of the radicals X_1 to X_5 is an imino group, is alkylated with a compound of the general formula

$W\text{-}Z_6$ (XV)

in which

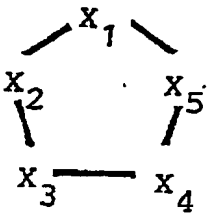
W is an A-B-C or R_bO-CO-E-D group, whereby A to D are defined as mentioned in claims 1 through 5, and

Z_6 is a nucleophilic leaving group, or

k) to prepare compounds of the general formula I, in which R_b is an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are as defined in claims 1 through 5, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to

3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety,

a compound of the general formula



(XVI)

in which

X_1 to X_5 are as defined in claims 1 through 5, with the proviso that R_b is a hydrogen atom, is esterified with a compound of the general formula

Z_7-R_b' (XVII)

in which

R_b' is an R_1-CO-O-(R_2CH)- group, in which R_1 and R_2 are as defined in claims 1 through 5, an alkyl group having 1 to 5 carbon atoms, an alkenyl group having 3 to 5 carbon atoms, a phenylalkyl group having 1 to 3 carbon atoms in the alkyl moiety, a cycloalkyl or cycloalkylalkyl group each having 5 to 7 carbon atoms in the cycloalkyl moiety and

Z_7 is a hydroxy group or a nucleophilic leaving group and,

if necessary, a protective group, employed during the reactions to protect reactive groups, is removed and/or,

if desired, a thus obtained compound of the general formula I is separated into its stereoisomers, and/or

a thus obtained compound of the general formula I is converted to its salts, particularly for pharmaceutical administration, into its physiologically tolerable salts, with an inorganic or organic acid or base.

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